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STUDIES ON THYROIDS*

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The results of four rather unusual kinds of study on the thyroid supply the basis for this discussion. Our studies have been made on doves and pigeons. These animals are peculiarly adapted to thyroid studies, since they feed exclusively upon the same dry grains throughout the year, and from them the complete reproductive history of all individuals is readily obtained.

SEASONAL VARIATIONS OF THYROID SIZE

The data obtained by Riddle and Fisher (1925) show that in three kinds of pigeons the thyroid notably and promptly enlarges in autumn and winter and becomes smallest in summer; a decrease in size begins promptly with the appearance of warmer external temperature in the early months of spring. It was shown in the paper cited that this result was obtained on material practically free from the complicating effects of diet, care, locality, race, age, length or degree of confinement, health, and body size of the animals examined.

The polygons of Figure 1, and that at the bottom of Figure 2, provide some hitherto unpublished data on the nature and extent of this seasonal change. Only seasonal *differences* are

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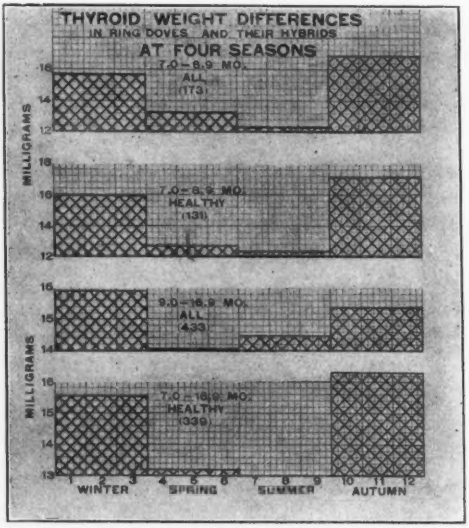
plotted on these polygons, but the values (abscissae) given provide exact information on the average size of the thyroids at each of the four seasons. The three months composing each season are of course here thrown together. Some irregularities in the seasonal averages may appear when, in addition to healthy birds, those infected with round worms (ascariasis) are also included in the averages (second polygon from bottom of Figure 1).



Though the animals which supplied these data were given considerable protection from cold, they were subjected to lower temperatures during the autumn and winter than during the remainder of the year. The common pigeons were kept in separate buildings from the ring doves and were supplied with less heat. Our data show a more pronounced seasonal change in the thyroids of common pigeons than in those of the ring doves.

The thyroids of doves and pigeons were found to increase with age. Only in birds older than 30 months was any sexual difference in thyroid size observable in our data—the average size of the female thyroids thereafter was somewhat larger. In diseased birds the thyroid size was more variable than in the

healthy. This study was based on careful weighings of 890 pairs (the pigeon thyroid is a paired organ) of thyroids. The histology of a few "winter" and a few "summer" thyroids have been examined. The winter thyroids show the more active and the summer thyroids the less active condition.

These results are free from certain objections which must be raised concerning the available data for seasonal thyroid change in mammals and man. Nevertheless the present and earlier data are in substantial accord.

In animals killed in an abattoir Seidell and Fenger (1913, 1914) found that the weights of fresh glands, as well as their iodine content, show a more or less regular seasonal change in cattle and sheep. Low and high iodine content were observed to correspond to winter and summer, respectively; but the size of the glands was more loosely correlated with winter and summer—due doubtless to the heterogeneous and largely unknown nature (age, size and source) of the animals supplying the thyroids. Herzfeld and Klinger (1922) have stated that data obtained by them on the thyroids of human (Swiss) subjects suggest an enlargement of this gland in winter. They also obtained higher percentages of iodine in summer, lower in winter; their data, however, are rather meager and by no means cover the various parts of the year.

In addition to the above data specifically based on season, the literature contains some observations on changes of size and histological appearance in the thyroids of animals subjected to periods of heat or cold. In rats kept on a controlled diet and exposed to cold during several days Cramer (1916) observed histological changes which are probably similar to those observable in "winter" thyroids of other animals. Mills (1918) likewise found both directions of change in the thyroids of rabbits, cats and guinea pigs subjected to heat or to cold during one to four weeks. Hart (1922) subjected a group of gray mice to heat, and others to cold, during a few weeks. A reduction of thyroid size was observed in the former group and evidence of increased function in the latter group. When individuals of either group were restored to normal temperatures it is stated that their thyroids soon regained their normal size and histological appearance. Finally, Adler (1920) observed that races of the grass frog (*Rana temporaria*) from higher

and colder (Alpine) regions have larger thyroids than those from warmer (Adriatic) regions; while those from an intermediate altitude and climate (Bavaria) have thyroids of intermediate size. In experimental cultures of tadpoles he also found atrophic thyroids in animals raised at high temperatures, while hyperplastic thyroids were found in those raised at low temperatures. On the other hand, it was elsewhere reported that in hibernating hedgehogs the size of the thyroid is decreased.

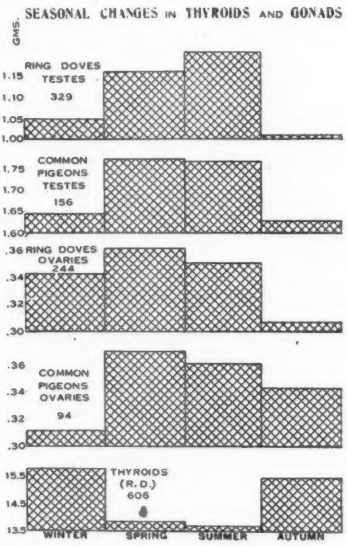
The facts now available unmistakably lead to the conclusion that the thyroids of non-hibernating higher vertebrates normally undergo enlargement in autumn and winter and become smaller during spring and summer; that these size changes are responses to the external temperature; and that the enlargement from this cause is accompanied by an increase of hormone-production in this organ.

In the application of these findings to normal and abnormal conditions of the thyroid in man various facts and observations will become uppermost in the thought of different investigators and clinicians. It is our wish further to note only that in primitive man, as in higher vertebrates generally, this seasonal rhythm of thyroid size and function was probably in full swing; and that—as shown in the next section—thyroid rhythm seems initially to bear a relation to gonad and reproductive rhythm. But civilized man in temperate and cold climates has probably partially defeated this primitive rhythm by wearing more clothing in winter, by building homes, and by supplying heat to these homes. Are there results or consequences of this repressed rhythm of thyroid function?

RECIPROCAL SIZE CHANGES OF GONADS AND THYROIDS IN RELATION TO SEASON

We may now examine the seasonal changes in gonad size in practically the same groups of birds which supplied the data just examined for thyroid size. When the two series of measurements are thus compared it is found that the periods (autumn and winter) of increased thyroid size are periods of decreased gonad size. On the other hand, the seasons (spring and summer) of reduced thyroid size are seasons of gonad enlargement. It is further found that the period of free or frequent ovulation in these same pigeons coincides with the

period of diminished thyroid size and of larger gonad size; the period of restricted ovulation—and also of more frequent reduction of the pigeon's clutch to a "single" egg—coincides with the period of increased thyroid and decreased gonad size. In Figure 2 are shown some hitherto unpublished data which establish these relationships. Other data will be found in an earlier study (Riddle, 1925).



From an inspection of these data it would at first seem obvious that the alternating or reversed seasonal changes in thyroid and gonad indicate antagonistic relationships between these two glands. Unless accompanied by certain reservations, however, such a conclusion does not seem necessary. The reasons are: First, in birds we are able at many points to distinguish sharply between *sex* and *reproduction*. And there is evidence that both thyroids and gonads in birds are intimately related to both sex and reproduction. Second, whatever may be said of single or multifarious functions of the thyroid, the gonad is both a reproductive and a sexual organ; and it is only a coincidence of increased thyroid activity with a diminution or suppression of an aspect of *reproduction* that is indicated by

our results. Third, other studies made in our laboratory make it seem probable that the antagonism involved in this repressed reproduction lies between the thyroid and suprarenal rather than directly between the thyroid and gonad. This point can not be discussed here. Fourth, some evidence af hand indicates that abnormally *small* thyroids as well as abnormally large ones are accompanied by decreased reproduction in (female) pigeons.

Nevertheless our data make it clear that size rhythms in thyroid and gonad do alternate in pigeons, and that the alternating periods of large size mean, in both these organs, periods of increase in an easily definable function. The season of largest thyroid size is its period of most active hormone production; and during this period the gonad—testis or ovary—is smallest and least active in its reproductive function. In summer these states are reversed. Common pigeons may reproduce during a dozen years, and it is practically certain that twice annually throughout this period the thyroid and gonad thus rhythmically and alternately increase their size and function.

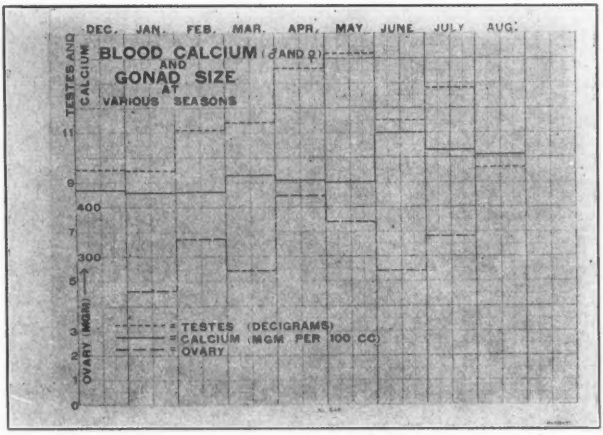
That this relationship of thyroid and gonad is not a chance or fortuitous one in these animals is made clear by many facts that could be cited. That a similar relationship extends beyond the two species belonging to two zoological families (*Columbidae, Peristeridae*) in which the point has been adequately investigated is perhaps a matter that will be conceded by all. Whether this simple relationship applies to man is yet to be investigated. The fact inviting such investigation is, however, at hand.

SEASONAL VARIATIONS IN PARATHYROID ACTIVITY (SERUM CALCIUM) IN RELATION TO THYROID AND GONAD

To whatever extent the level of the serum calcium may indicate parathyroid activity we are also able to examine the question of seasonal changes in the parathyroid. Moreover, since the weights of the thyroids and gonads were at once obtained on the same individuals which supplied the data for blood calcium, it is possible to plot the size of these organs against the calcium values. Unfortunately, the available data do not represent numbers large enough to make it certain that the curves tell an entirely true story. These data were obtained rather incidentally to a more serious investigation of blood cal-

cium changes in the reproductive cycle (Riddle and Reinhart, 1926).

The relation of season to the blood calcium of healthy adult ring doves of both sexes is shown in Figure 3. The values are plotted by months. One finds a fairly distinct increase of blood calcium in spring and summer over the values obtained in winter. On the same figure we have plotted the weights of the thyroids of the particular birds which supplied the calcium values in the various months of the year. It will be seen that these particular thyroids tend to become smaller during those months (June excepted) characterized by increased calcium

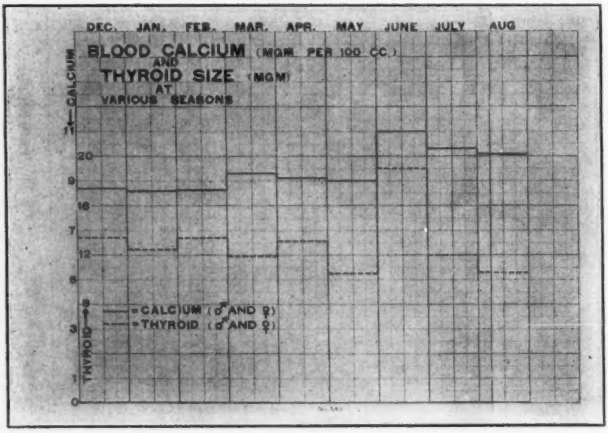


values. Only 55 thyroids are included in this curve, but reference to the more extensive data on this subject—already discussed at the beginning of this paper—will show that this curve for thyroid size accurately represents (apart from the exceptional status of June) the normal seasonal change in the thyroids of pigeons. The data of Figure 3 indicate that the season of apparent high blood calcium in pigeons is certainly the season of low thyroid size, and *vice versa.*

In Figure 4 the curve for seasonal change in blood calcium is again reproduced, and the size of the ovaries and testes of the particular birds which supplied the calcium data are plotted against the calcium curve. Here it will be observed that periods of low blood calcium coincide with periods of smaller size

in ovary and in testis. Although the data given here for testis and ovary are rather inadequate, because of limited numbers and the considerable size variability in these organs, an adequate amount of earlier evidence—also discussed above—shows that the seasonal change of ovary and testis which is indicated here is typical and normal.

Our evidence for a seasonal change of the blood calcium level is somewhat strengthened by two earlier observations that have been made on seasonal change in blood phosphates and in the size of the parathyroids. The value of the seasonal change in phosphates as evidence on our present topic lies in the cir-



cumstance that in healthy individuals blood phosphorus and blood calcium usually tend to change in the same direction. Hess and Lundagen (1922) found in the blood of infants a low percentage of phosphorus in winter and a high percentage in summer; and this effect is attributed mainly to the seasonal variations of sunlight. This is precisely the relationship that we find for season and calcium. Still more closely identified with the present topic are the results obtained on rabbits by Grant and Gates (1924), who noted a marked diminution of size in the parathyroids between November and February. Further, treatment of the animals with ultra-violet light produced more notable size changes in the parathyroids than in other

organs—the parathyroids becoming markedly enlarged. Grant and Gates (1925) also carefully studied the blood calcium of the treated and untreated rabbits, but an effect of caging or confinement was found which served to complicate their data for seasonal change. These investigators have hesitated to draw a conclusion as to a seasonal change of blood calcium, and emphasize rather that "a parathyroid hypertrophy of 20 to 50 per cent does not result in a corresponding increase in the calcium content of the blood when the concentration is already at or near the normal level." They find that in general the blood calcium and phosphorus tend to change in the same direction.

Evidence for a seasonal change in the level of blood calcium is thus found in our own data and in the data of other workers. In immature pigeons lower values were found in winter and higher values in summer. In the pigeon it is known that the testes and ovaries undergo a size change in the same direction as the serum calcium, and that the thyroid is largest at the time the serum calcium is at its minimal seasonal value.

THE ESTABLISHMENT OF RACES OF PIGEONS WITH CHARACTERISTICALLY LARGE AND WITH CHARACTERISTICALLY SMALL THYROIDS

A fourth, and very important line of study has been concerned with the establishment of races or strains characterized by large or by small thyroid size. This investigation must be fully described elsewhere (probably in the American Naturalist), and only a short statement concerning the main result can be given here.

At the outset we had a rich variety of material, both in common pigeons and in ring doves, from which to undertake this study. Numerous individuals with normal and others with various types of abnormal reproductive performance were at hand. Two years of previous study had led to the conclusion that these various types of reproductive disturbances were ascribable to neither nutritional deficiency nor to infection. These exclusions directed attention to their probable origin in endocrine disorder. It was therefore decided, now nearly six years ago, to learn what had already unintentionally been done, or could later purposefully be done, toward establishing definite "thyroid" races in these mongrelized birds—races permanently characterized by large or small thyroid glands.

It must be said that it is still too early to evaluate the relative importance of the earlier breeding history as compared with the definitely directed procedures of the past five years; and we further realize that the whole subject is much complicated and that thus far we have only imperfect knowledge of the sources of temporary, as distinct from hereditary, thyroid-size variations. Nevertheless, it is evident that we now have "large thyroid" races and "small thyroid" races of ring doves. For individuals belonging to one of these strains or races it is

TABLE I

ESTABLISHMENT OF "THYROID RACES" IN RING DOVES

	Race	Generation	Parents and Offspring	No.	Group Averages		
					Age (mo.)	Body Weight (grams)	Thyroids mgms.
With LARGE thyroids	162	F_1	Parents.....	2	62.1	174	22.7
			Offspring.....	16	14.2	166	20.3
		F_2	Parents.....	9	16.7	170	20.9
			Offspring.....	28	11.7	158	20.9
		F_3	Parents.....	4	16.9	165	27.4
			Offspring.....	14	17.8	159	24.7
		F_4	Parents.....	2	26.7	152	25.5
			Offspring.....	4	11.1	157	25.0
	311	F_1	Parents.....	2	92.0	(165)	38.3
			Offspring.....	10	15.9	160	20.3
		F_2	Parents.....	8	16.4	159	18.4
			Offspring.....	15	14.9	152	19.2
		F_3	Parents.....	6	19.1	148	16.8
			Offspring.....	8	12.3	147	17.4
		F_4	Forced to continue race by crossing F_3 with out three-fourths pure 311.				t-cross only
With SMALL thyroids	36	F_1	Parents.....	2	89.8	165	15.0
			Offspring.....	5	16.0	158	12.9
		F_2	Parents.....	2	18.0	160	12.1
			Offspring.....	15	13.0	159	11.1
		F_3	Parents.....	6	17.9	157	11.6
			Offspring.....	21	10.9	146	13.0
		F_4	Parents.....	2	20.0	174	11.8
			Offspring.....	1	13.8	140	12.1
	161	F_1	Parents.....	2	50.8	186	15.0
			Offspring.....	31	17.7	171	13.8
		F_2	Parents.....	4	19.8	167	11.0
			Offspring.....	10	21.3	166	12.5
		F_3	Parents.....	4	25.0	171	13.0
			Offspring.....	9	16.2	(165)	12.1
		F_4	Parents.....	2	30.6	160	11.0
			Offspring.....	2	10.6	160	11.1

now possible—on the basis of pedigree only—to predict the presence of thyroids larger or smaller than normal.

Summaries for four such races are given in Table 1. Two strains or races of ring doves with large thyroid size, and at least two races with small thyroid size, appear to have been established. Through four successive generations a great majority of the healthy individuals of these races have shown thyroids characteristically large or small in accord with their race. We have fifteen or twenty ring dove races whose thyroids are of intermediate size.

Concerning the interest and importance attaching to this result it may be noted that this is the first time that a race characterized by the size of an endocrine organ has been obtained in genetical study. It is further notable that in many respects human races and nationalities are the genetic or biological equivalents of the races upon which our studies have been made. The possibilities of the establishment of races or strains of one or another thyroid size are, theoretically, similar in the two forms; the advantages, perils and disadvantages to a race of an hereditarily large or small thyroid are already susceptible of examination in these races of pigeons. Such studies are already being made. We now make no statement as to whether the large thyroids exhibit hyper- or hypo-function. Our laboratory, in collaboration with Professor F. G. Benedict, will soon resolve this question by studies now in progress on the basal metabolism of these "thyroid" races.

SUMMARY

The thyroids of various species of pigeons undergo a functional enlargement during the autumn and winter months and a progressive decrease in size during the months of spring and summer. These changes follow as prompt responses to the external temperature.

In various kinds of doves and pigeons both testes and ovaries enlarge during the spring and summer, and decrease in size during the autumn and winter. This is precisely the reverse of the seasonal size changes in the thyroids of these same animals.

If seasonal changes in the serum calcium level represent changes in parathyroid activity this organ is probably more active during spring and summer than during winter. Great-

est parathyroid activity thus coincides with greatest gonad activity and with lowest thyroid function.

Races of doves characterized by large thyroid size, and other races characterized by small thyroid size, have been successfully established.

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HOW FAR CAN RECENT STUDIES ON THE OVARIAN FOLLICULAR SUBSTANCE BE APPLIED TO THE HUMAN? A BRIEF DISCUSSION OF THE THERAPEUTIC ASPECTS OF THE PROBLEM*

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In 1923 Loeb made the statement that "while the evidence concerning the maturing follicles as the cause of the changes in the first phase of the sexual cycle is not as definite as the evidence relating to the significance of the corpus luteum in the second phase, still, as it stands at present, the evidence points very strongly to the conclusion that the maturing follicles or the follicles nearing the stage of maturation dominate the first phase in the same way as the corpus luteum dominates the second phase." The interesting series of studies published during the past few years seem to have almost completely reversed the view enunciated by Loeb, for certainly the recent trend has been to stress the role of the follicular fluid and to minimize that of the corpus luteum.

The purpose of this communication is merely to set forth the reaction to these recent studies of one who has been more particularly interested in the study of the human reproductive cycle. The deep interest of gynecologists and obstetricians in the laboratory study of the sexual cycle in the lower animals is easy to understand, when one considers the difficulties of the experimental approach in the study of menstruation in women. The fact that our friends the anatomists and physiologists have taken such vigorous hold of this problem bodes well for far more rapid progress along this line than would otherwise be possible.

At the outset I may say that the views of Loeb on the relative importance of the follicles and the corpus luteum harmonize much more readily with what we know of the human problem than do those of Allen and his co-workers, Frank and others,

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important and accurate as these studies no doubt have been. It has seemed to me that, in applying animal results to the human problem, too little cognizance has been taken of the important differences between the sexual cycles of the lower animals and the human female. In many of the lower animals, such as the rat, the cycle is unquestionably dominated by the follicle. Oestrous phenomena are readily produced in spayed animals (Allen and Doisy) or those which are immature (Frank and others) by the injection of follicular fluid. But these phenomena are not easily comparable with those observed in the human female, from either an anatomical or a physiological standpoint.

To bring out this fact, let us for a moment review the conception of menstruation which has come to be quite generally accepted by gynecologists and obstetricians. This conception, I may add, is not by any means speculative, nor does it represent a blind acceptance of the views enunciated by Fraenkel in 1903 as to the importance of the corpus luteum in the physiology of the process. It is based chiefly upon careful histological and clinical correlation of the ovarian and endometrial cycles. It is to this method of study, for example, that we owe our newer knowledge of the time of ovulation, which is now accepted as occurring, not at the time of menstruation, as was formerly believed, but at approximately the thirteenth or fourteenth day of the cycle, with considerable individual variation in different women.

The ovum, after its discharge from the follicle, begins its passage down the Fallopian tube, this requiring several days at least. In the meantime the endometrium is making preparations for its reception. In the immediately post-menstrual phase the endometrium is thin, but it undergoes a steady development from day to day, probably under the influence of the maturing follicles, for the old corpus luteum is now definitely retrogressive, and the new one is in its early formative phase. The glands, at first narrow and collapsed, increase in width and tortuosity, this continuing throughout the long interval phase up to a period of four or five days before the next menstrual hemorrhage. During this time the corpus luteum is steadily developing, reaching its mature phase four or five days before the period, and its histological appearance, at least, suggests a definite incretory function.

It is during this phase of the corpus luteum that we find a picture in the endometrium which can scarcely be construed as a mere advance on the preceding slow hypertrophy, for an entirely new feature is added. For the first time the glandular epithelium presents striking evidence of secretory activity, be-

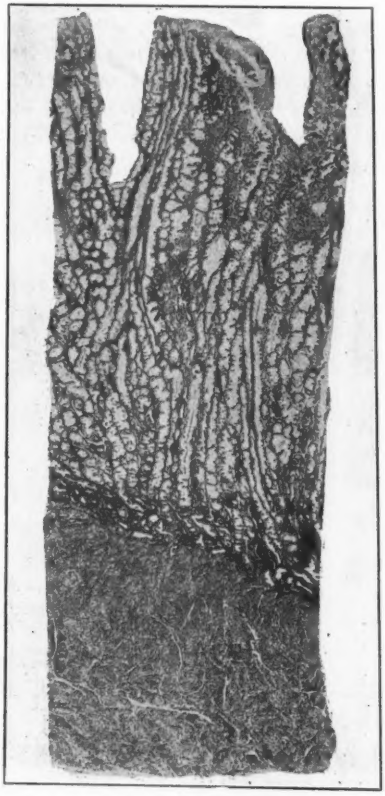

Fig. 1. Typical human premenstrual endometrium, with which one characteristically finds (I have encountered no exception) a mature corpus luteum in the ovary. Note secretory change in gland epithelium.

coming low and frayed, the cells often melting away into a mucoid secretion within the lumen. This characteristic is so striking that it can be recognized at a glance, and this phase is, indeed, commonly alluded to as the secretory phase (Fig. 1).

So far as I have been able to gather, such a picture is not encountered in the laboratory animals where sexual cycles have been recently so extensively studied. This statement will apply, I blieve, to both the normal oestrous cycle and those produced artificially by injections of follicular fluid.

Certainly the photographic representations of the endometriums of monkeys in these phases, as given by Allen, bear no resemblance to the premenstrual endometrium of the human. Indeed, the only exception to this general statement is to be found in one of the cases pictured by Corner in a forthcoming paper, which he has kindly placed at my disposal (Fig. 2). In this case the histological picture can not be distinguished from

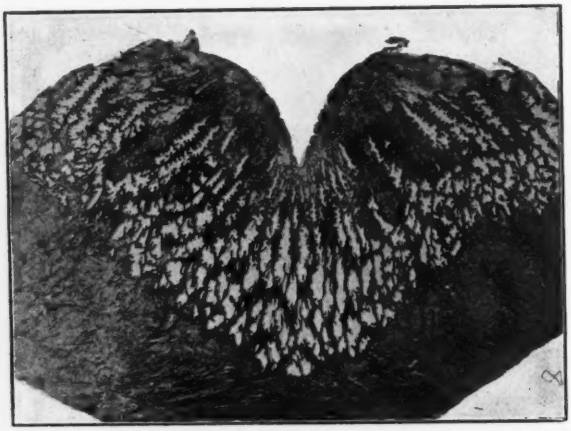

Fig. 2. Premenstrual endometrium in monkey, associated in this case with the mature corpus luteum in the ovary, as in human. This picture is exactly like that found characteristically in the human (see Fig. 1), although this type of premenstrual change appears to be less common in the monkey than that shown in Fig. 3. For this picture I am indebted to Dr. George W. Corner.

that characterizing the premenstrual endometrium in the human. The significance of this will be discussed later in this paper.

Does not this common lack of the secretory phase in the lower animals suggest that the corpus luteum is the factor responsible for this topping-off of the endometrial development, rather than the growing follicle, which now, indeed, is almost at its ebb? In other words, at the time when the endometrial changes reach their acme the development of the follicles is far

less advanced than it is just before ovulation, which takes place about two weeks later. And yet, just before ovulation, when the follicle is fully mature, the development of the endometrium is at a relatively low ebb. I am aware, of course, that other follicles than the dominating one of that particular cycle may conceivably be concerned in the premenstrual hypertrophy, but to assume that their influence at times overshadows that of the presiding follicle and at other times is subordinated to it presupposes an interfollicular antagonism which appears highly illogical, and, so far as I know, has no scientific support.

On the basis of observations upon laboratory animals, the current trend appears to be to doubt that ovulation is a necessary precursor of menstruation. This skepticism has much to support it in the case of the lower animals, but very little in the case of the human being. Especially interesting, in this connection, has been the study made by Corner of the sexual cycle in monkeys, in which there occurs a menstrual cycle readily comparable with the human process. In his study of a series of monkeys (Macacus rhesus), in 1923, Corner found that in a considerable proportion no corpus luteum was to be found in the ovaries when these were removed immediately after what was apparently a genuine menstrual flow, and he therefore very properly questioned whether the corpus luteum plays any part in the process.

As far back as 1906 van Hewerden, in the autopsy study of a rather large series of monkeys, made the same observation. From this standpoint this author divided the animals into two groups. In one the uterine mucosa shows marked premenstrual swelling, with striking tortuosity of the glands, and definite secretory characteristics. In all the animals of this group prominent follicles or well developed corpora lutea were found in the ovaries. In the other group, the endometrium was thin, and the premenstrual swelling much less noticeable, while the glands showed none of the cork-screw tortuosity found in the other group. Furthermore, corpora lutea were not seen in the ovaries.

Corner's paper, in which he suggested the possibility of menstruation without preceding ovulation, has been answered by Robert Meyer, who pointed out, among other things, that it was difficult to be sure that the bleeding observed in Corner's

monkeys was in all cases analogous with normal menstruation. In the human female we likewise not infrequently encounter a form of pseudo-menstrual bleeding in which corpora lutea are not only absent, but characteristically so. This form of abnormal menstruation is very common in women near the menopausal epoch, but may occur at any age during the reproductive years. It is not rare at or near the time of puberty.

As already mentioned, the characteristic findings in the ovaries of such cases are an absence of corpora lutea, and the presence of a persistent unruptured follicle, or, perhaps, of many maturing follicles. I believe that in such cases we are actually dealing with a follicular type of cycle, which persists in a vestigial way in certain individuals.

But this is certainly not the usual process observed in human females. Every gynecological pathologist will discredit this assumption. The examination of thousands of ovaries, in correlation with the endometrial changes and the menstrual histories, has convinced me of the regularity and normality of our findings in this respect. Just after menstruation we expect to find, and do find, the characteristic undeveloped endometrium (post-menstrual type) and, in the ovary, a retrogressing corpus luteum; in the interval phase we find a slowly developing hypertrophy of the endometrium, and, in the ovary, a corpus luteum showing more advanced retrogression. Moreover, it is in this stage that we find the earliest stage of the new corpus luteum resulting from the rupture of the mature graafian follicle. Again, in the few days just before the next menstrual period we confidently expect to see the pregravid or secretory endometrium above described, and, in the ovary, a typical mature yellow body. Finally, the period of menstrual casting off of endometrium is accompanied by beginning retrogression of the corpus luteum. These observations have been made in so many laboratories by so many men that they must be accepted as authoritative evidence, just as we accept the quite different results obtained in the lower animals by the anatomists and physiologists.

For certainly this histological cycle does present important differences from that seen, for example, in the rat, in which the cycle is apparently fully run under the influence of the follicle alone, and in which it can be reproduced, in the spayed

animal, by injection of follicle fluid alone. The relatively infrequent form of uterine bleeding above alluded to, in which corpora lutea are absent, constitutes the exception and not the rule. This type of menstruation is characterized especially by its excessiveness (functional menorrhagia), and this is presumably due to the absence of the corpus luteum, which normally exerts an inhibitory effect upon the further maturation of follicles.

It is possible that, in rare instances, even a normal menstrual flow in the human may occur without ovulation; that is, that it

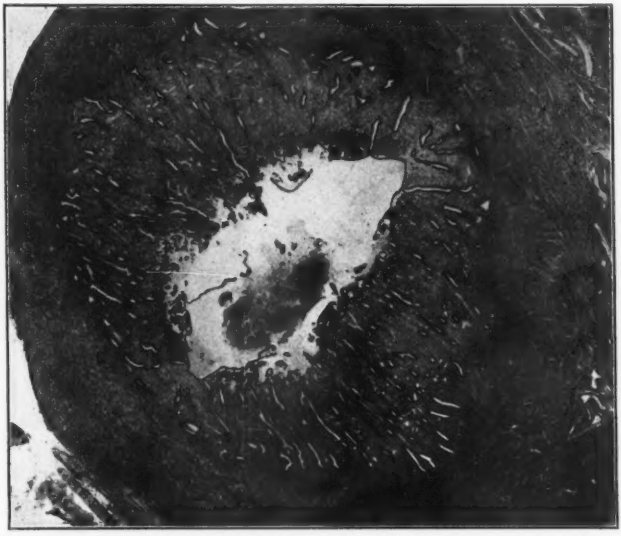

Fig. 3. Type of endometrium found just after onset of menstrual bleeding in monkey, with no corpus luteum in the ovary, but, instead, a mature Graafian follicle. This association appears to be more common in monkeys than the corpus luteum type, shown in Fig. 2. For this picture I am indebted to Dr. Carl Hartman.

may be due to the influence of the follicle alone. Until recently such a view would have seemed untenable to me, and even now I know of very little direct evidence to support it. But the splendid researches of Corner, Allen and Hartman upon monkeys, and the knowledge that in the human being a form of uterine bleeding, often definitely periodic, may be due to follicular influ-

ence in the absence of corpora lutea, makes it difficult to deny the possibility above alluded to.

Much light is thrown upon this problem by a study of the endometrium just before menstruation in monkeys. As already mentioned, Allen's illustrations show no such condition as we find in the human at this phase. Corner also emphasized this fact, and, in his forthcoming paper, speaks of two different kinds of premenstrual endometrium. One is essentially similar to the human and follows ovulation by about twelve or fourteen days. The other is devoid of the premenstrual features seen in the human, and apparently is not dependent upon a preceding ovulation. The latter is the more frequent type in monkeys, but the menstrual bleeding in the two groups of cases is apparently indistinguishable in type. The second type, which we may for convenience allude to as the follicular type, is well illustrated in Fig. 3, for which I am indebted to Dr. Hartman. This endometrium was obtained from a monkey just after the onset of menstrual bleeding. A large follicle was found in the ovary, but no corpus luteum.

Knowing the accuracy of these observations of Corner and of Hartman, the conclusion seems inescapable that in the monkey either one of two types of cycle may occur. One is dependent upon ovulation, and in this the corpus luteum plays an important role, part of which at least is the production of a pregravid endometrium similar to that seen in the woman. In the second type, ovulation is apparently not essential, and in this the corpus luteum plays no known part, while the endometrium fails to show the markedly hypertrophic and secretory changes characteristic of the human premenstrual phase.

As already mentioned, there can be no doubt that in the human female the prevailing mechanism of menstruation is of the first of the two types above mentioned, *i. e.*, the corpus luteum type, as it may be spoken of for convenience. The evidence for this seems overwhelming. There are, it is true, a few scattered observations in the literature tending to show that menstruation may occur without ovulation and corpus luteum formation. Most of these, however, are unconvincing. And yet, as already stated, it would be strange if the follicular type of menstrual cycle did not occasionally persist in the human species. A recent observation of my own is suggestive, though not conclu-

sive. A young woman of 19 whom I had treated for two years for functional menorrhagia was taken with acute appendicitis, so that an opportunity was given to inspect at least hastily the ovaries, as a right rectus incision was employed. I may add that, whereas her periods had formerly lasted for as much as two or three weeks and had been very profuse, the two or three periods immediately preceding the operation were much more moderate, lasting only four or five days. There had been no flow for two months until the day before the operation, when a slight menstrual show appeared. At operation the right ovary presented a large translucent follicle, evidently mature. No sign of a corpus luteum could be seen in this ovary nor in the left. The day following the operation menstrual bleeding was resumed quite freely. This case suggests that the responsible factor was the large mature unruptured follicle, as, in my experience, a mature corpus luteum can usually be detected even by simple inspection of the ovarian surface. Certainly none could be found in this case. This is the only instance which I have personally observed which would shake my belief in the invariability of the rule that menstruation cannot occur without a corpus luteum, *i. e.* without a preceding ovulation. I believe, however, that more careful observation may conceivably show such cases to be less rare than I now believe them to be.

It would hardly seem necessary here to dispel a superficial misconception held by some of our profession to the effect that the corpus luteum is responsible for menstruation, applying the latter term to the actual bleeding of the process. This structure, of course, has nothing to do with the direct causation of the menstrual discharge itself. Indeed, menstrual bleeding occurs not because of, but in spite of, the corpus luteum influence. The latter, we believe, is responsible for the final and characteristic secretory developmental phase. If the corpus luteum influence persists undisturbed, as when pregnancy supervenes, the endometrial hypertrophy advances still further to genuine decidual formation. But if the corpus luteum influence is checked, as it is when fertilization fails and the ovum of the preceding ovulation reaches the end of its life span, then its protective influence over the growing endometrium is removed and the endometrium dismantles itself, with bleeding as a chief accompaniment.

These statements are here set forth rather baldly, but they are supported by much evidence, except for the assumed influence of the ovum itself. We have no way of determining this point, and yet, a cell with such amazing potentialities as the ovum may well exert profound influences even before fertilization. How else can we explain the remarkable periodicity of the menstrual phenomenon than by ascribing it to some innate quality of the germ cell itself?

The above conception of menstruation and of the role of the corpus luteum is borne out by certain observations which can be made in the gynecological operating room. I have often noted that if, in a woman operated upon several days before the expected onset of menstruation, it becomes necessary to remove the ovary containing the corpus luteum, menstruation is precipitated, *i. e.* it occurs soon after the operation, often within a matter of twelve to twenty-four hours, and rarely later than forty-eight hours. As far back as 1911 Neu made somewhat similar observations, although he did not correlate them with the corpus luteum, which was just becoming an object of intensive study.

The explanation of such an anticipation of the normal menstrual date would seem to be in the removal of the corpus luteum influence, just as it normally is checked by the death of the ovum, if this be actually the dominating factor. It is, of course, conceivable that the premature onset of menstruation in such cases may be due to the nervous shock of the operation. This can be readily controlled by studying the effect upon menstruation of pelvic operations in which the corpus luteum is not disturbed. I have done this systematically only since beginning the preparation of this paper, but the small series of observations thus made, together with the general impressions gained over many years before this, makes me feel very strongly that it is the corpus luteum factor which is concerned with this disturbance of menstrual rhythm.

There are one or two discordant observations noted in the studies of those who consider the follicle the dominating factor in the menstrual cycle. For example, Allen, in a forthcoming complete study of the cycle in monkeys, which he has generously allowed me to read in manuscript form, states that "reddening of the skin of the vulva and surrounding regions, the

'sexual skin,' was usually present to some degree during the whole menstrual cycle. It often became intense during the interval.'' Dr. Carl Hartman, of the Carnegie Institute of Embryology, who is now studying the reproductive cycle in a considerable colony of monkeys, makes the same observation, and has very generously demonstrated to me this and many other aspects of the problem. But this deepening of the sexual skin is presumably due to the increasing intensity of the follicle influence, which reaches its acme just before ovulation, *i. e.* at about the thirteenth or fourteenth day of the cycle. Does it seem probable that this same follicle influence which now begins to wane, if one may judge by the sexual skin change, would nevertheless be responsible for the endometrial hypertrophy, which now for the first time begins to become pronounced. At menstruation, it may be added, the sexual skin fades, so that the hue is lighter than at any other period in the cycle.

It is of interest to note, also, that the ovaries of young children, or even of foetuses, show varying degrees of follicular maturation, so that some of the follicular cysts contain considerable amounts of follicular fluid. Corpora lutea are, however, never present. The reproductive cycle does not make its appearance until the still unknown impulse of puberty appears, after which corpora lutea are of course constantly found under normal conditions. This, of course, may be construed as only bearing out what Allen has emphasized, *i. e.*, the follicle is capable of exerting its influence only when it reaches a certain stage of maturity. Otherwise it would be difficult to conceive of its exerting any cyclical influence, inasmuch as there are in every normal ovary during reproductive life a greater or less number of follicles in various stages of maturation.

The general impression which one gains from a consideration of the facts which have been discussed is that a sort of evolutionary gradation of the reproductive cycle has been demonstrated in the results already obtained with the various animals already studied, a gradation not unlike that exhibited by other body functions. In such animals as the opossum and rat, the evidence certainly indicates that the cycle is dominated by the follicle and that the corpus luteum does not become important until after impregnation. In the human, on the other hand, the follicle is of importance in the menstrual cycle, but so is the

corpus luteum, which is well developed in the non-pregnant woman.

Finally, the observations thus far made on monkeys, chiefly by Corner and by Allen, suggest that in these animals an intermediate condition exists, so that in some the follicular type persists, while in others there has been an advance toward the human type. For that matter, it would seem that one and the same animal may at different ages and under different environmental conditions, exhibit differing types of cycle. Even in the human being, if the views I have advanced be correct, there would at times appear to be a persistence of the more primitive follicular form of cycle.

After all, as Meyer says, unless our conception of the teleology of menstruation is all wrong, it would be surprising if the corpus luteum played no part in primary menstruation. If the premenstrual change in the endometrium is really a pre-pregnancy or pre-decidual modification, and if, as is commonly accepted, the corpus luteum plays a definite role in early pregnancy, it would require stronger evidence than now exists to convince one that the corpus luteum of menstruation is not also an important incretory organ. Histological evidence at least would suggest that just as the predecidual endometrium is by an easy transition converted into genuine decidua, so the corpus luteum of menstruation likewise passes directly over to the corpus luteum of pregnancy. It is hard, also, to deny that these two endometrial stages are not both due to the influence of the corresponding phases of the corpus luteum.

The corpus luteum is, in a sense, only a glorified follicle, and it is easy to believe that the function of the follicle is carried as a hang-over into the earlier stages of the corpus luteum. This is, indeed, borne out by the more recent investigations of Allen and others, who find the follicular principle in early but not in the late corpora lutea. But, just because the mature corpus luteum contains none of the follicular element, are we justified in assuming that it has no function whatever in human menstruation? Such a stand is untenable, even though, for the time being, injection experiments with corpus luteum derivatives have proved comparatively unfruitful.

An exception to this statement may be noted in the classical studies of Loeb and the recently published observations of

Papanicalaou. The latter, for example, was able to bring about striking acceleration of ovulation in guinea-pigs by the removal of the corpus luteum, and corresponding retardation of the process by the injection of lipoid-containing corpus luteum extracts. He discounts the importance attached by some to the findings of the follicular hormone in the corpus luteum, inasmuch as the latter apparently produced two hormones. The follicular substance, he believes, is "probably secreted by the undifferentiated theca or granulosa cells, while the specific luteal hormone is probably formed by the fully differentiated luteal cells, the latter increasing in number with the advancing differentiation and development of the corpus luteum."

This explanation, to my mind, is the proper answer to the claims made by Frank and his co-workers as to the unity of action of the follicle, the corpus luteum, and the placenta (the "gestational gland"), based chiefly on the fact that extracts from these organs are synergistic along certain lines. Such an assumption is unwarranted, not only because of the human evidence already set forth, but also because of the demonstration by Papanicalaou of a luteal hormone which possesses a function in many respects quite antagonistic to the follicle substance.

That these two hormones represent a sort of balancing mechanism is indicated furthermore by the recent investigations of Margaret Smith, who was able quite constantly to bring about an interruption of early pregnancy in rats by the injection of follicular extracts. It is during early pregnancy that the corpus luteum shows its most striking growth and is generally conceded to exert an important protecting influence upon the embedding of the fertilized ovum. As Smith says, "It seems quite improbable that the active part of the follicular fluid and the substance produced by the corpus luteum are identical, if the follicular extract injected at this time interferes with the normal development of the fertilized ovum."

As additional evidence against the view that the follicles and the corpus produce only one substance, and that the same, Smith mentions the difference in the effects produced by follicular injections upon ovariectomized and normal rats. In the former, injection soon results in the appearance of cornified epithelial cells in the vaginal smear, and if the injections be kept up daily for two weeks, these cornified cells persist throughout

that time. In the normal rat, however, such an effect cannot be produced, for even though the injections be kept up the normal cycle asserts itself, as reflected in the vaginal smears. The only explanation of this fact would seem to be that the normal ovary contains some element which balances or antagonizes the follicle influence, and which, of course, is lacking in the spayed animal. It seems reasonably certain that it is the corpus luteum which plays this role. Smith mentions an observation which bears out this idea. In four apparently normal animals the follicle injections produced an effect similar to that characteristically found in castrated animals, as above mentioned. Two of these animals were autopsied and their ovaries found to contain large follicular cysts, but no corpora lutea.

May it not be that, in most women at least, the corpus luteum principle is efficacious only in an endometrium already prepared by the follicular substance, as it apparently is under natural conditions? I am speaking, of course, of the human female, because in such animals as the rat, as already stated, the cycle appears to be dominantly a follicular one, the corpus luteum being perhaps more important after the inception of pregnancy. This idea will be alluded to again in the discussion of the therapeutic aspects of the problem.

As might have been expected, one of the earliest results of this newer work on the physiology of the ovary has been an effort to apply it clinically. No criticism can be made of such an ambition, provided that the therapeutic research is based upon sound scientific principles. In spite of the incompleteness of our knowledge of the subject, it is only fair to state that the recent work discussed in this paper offers, perhaps for the first time, something very tangible for clinical experimentation upon the human, and such observations will yield just as valuable evidence along certain lines as will the study of laboratory animals.

It is not my purpose to report statistics as to my results in the comparatively small group of cases which I have thus far had occasion to treat in the light of this newer work, but rather to comment upon certain new viewpoints which these investigations have appeared to inject into the practice of gynecological organotherapy. My views on the general subject of ovarian therapy,

and they were rather pessimistic, were expressed in a paper which I presented before this Association in 1922.

The chief indications for the use of follicular hormone would appear to be those associated with hypofunction of the ovary. The most important of these are amenorrhea and the subjective symptoms of the menopause. To these may perhaps be added certain types of obesity and certain cases of sterility. Neither of these two latter conditions, however, is associated in a very clear cut way with ovarian deficiency, while the first two named are, and it is to these two alone, *i. e.* amenorrhea and menopausal neurosis, that I have thought it best to limit my own discussion.

The preparation of follicular hormone which I have used is that made by Parke, Davis & Co., to whom I am indebted for a supply of the preparation for experimental use. The substance, as most of you know, is prepared by a technique similar to that recommended by Allen and Doisy, and is standardized on the rat unit basis. At first the ampoules contained only a few rat units, but more recently the strength has been greatly increased, to even 100 units per ampoule, although some deterioration of these stronger preparations is said to occur. No rules can be laid down as to dosage. From a practical standpoint, a daily injection is as much as we can expect the ordinary patient to take, so that, with the earlier weak preparations, the total dosage would seem to have been wofully inadequate.

Amenorrhea of the so-called functional type would appear to constitute the most trustworthy test for the efficacy or inefficacy of the treatment, for here the hoped for results are distinctly objective. At the outset I may say that I have not been able to produce menstruation by the injection of follicular hormone in any of the dozen or so cases which I have thus treated. In most of these, I should say, the extract used was quite weak (varying from 10 to 25 units per ampoule). More recently, however, a much stronger preparation was available, but the results have been the same. Nor have I been able to convince myself of any such noticeable increase in the size of the uterus as Allen and Pratt have reported in a few cases.

These failures were not surprising to me, inasmuch as I have always felt that the follicle hormone, important as it may be, can scarcely be expected to carry the histological cycle of the endometrium to the point where the ensuing involution would

be apt to produce a menstrual hemorrhage. It is conceivable, of course, that very strong dosage over many days might actually cause a hemorrhage of the type described earlier in this paper as of probably follicular causation, *i. e.* the so-called functional uterine bleeding. But I have personally not observed such a result, although a small number of successful results have been reported by others.

More recently I have been attempting to imitate what I believe are the steps occurring in the normal menstrual cycle. As already indicated, it is probable that in the human being the follicle produces the first phase of the cycle, and that the corpus luteum then takes up the process, carrying it up to the time of actual menstrual bleeding. It seems plausible to assume that neither follicle extract nor corpus luteum extract alone can fill the bill—that the follicle produces an effect which is usually insufficient for menstruation, and that the corpus luteum extract exerts its effect only in an endometrium already partially transformed by the follicle influence. A logical plan, therefore, would seem to be to give follicle extracts for a good many days, and then to inject corpus luteum extract, if a good one can be found. At my suggestion, the biological department of Parke, Davis & Co. were good enough to prepare a lipoid-bearing corpus luteum extract, this being done by two methods.

These extracts were prepared essentially by the same methods that are known to yield the active lipoids from other parts of the ovary as, for example, from the follicular fluid.

(a) Extract Hog Corpora Lutea.

Ground corpora lutea were allowed to stand over night in two volumes of 75% alcohol. This was filtered, and the residue extracted with hot alcohol (95%). The extracts were combined and distilled in vacuo. The residue was extracted with ether, and after removal of the ether the extract was emulsified in water, in the ratio of 1 cc. emulsion to 4 gm. ground corpora lutea. No physiological standardization was made.

(b) Corpus Luteum Lipoidal Extract.

The method of preparation was the same as the above, except that the ether extract was purified with acetone, and the final emulsion was in a 0.05% solution of sodium bicarbonate. One cubic centimeter of emulsion represented 4 gm. corpora lutea. The estrus-producing power of this extract was approximately 1 rat unit per cc., thus showing that some of the follicular hormone was present. The extract was not tested for corpus luteum activity since no definite method is as yet available for testing this type of activity. For this

reason the extract was put up on the basis of 4 grams of fresh gland to each 1 cc. of final emulsion.

Only six cases have been treated by this method, but it is in this small group that I have observed the most encouraging results. In two of these, menstruation has apparently resulted from a series of injections of follicular extract, followed by a series of injections of the corpus luteum extract. In one case the amenorrhea had been of only four months' duration, so that the importance of the injection in the subsequent menstruation appears less striking than it might otherwise be. This patient was twenty-six years of age, and her amenorrhea was of the so-called hypopituitary type. It was associated with a moderate degree of recently acquired obesity. A menstrual flow lasting three days followed the daily injection for twelve days of the follicle substance, followed by six daily injections of the corpus luteum extract. It is interesting to note that the flow appeared only after the injection of two more follicle substance injections, in a second series following the corpus luteum injections. This case is a recent one, and I merely mention it without any particular stress, as I have not been able to prevail upon the patient to submit to further observations along this line.

The other case, to my mind, is somewhat more impressive. The patient, a trained nurse of 36, had always been irregular in her menstrual history, with periods of amenorrhea lasting as long as six months. Three years ago, however, the periods ceased entirely, and there had been occasional vasomotor flushes, suggesting a premature menopause. There had been no increase in weight. Daily injections of follicle substance alone were given without result, so that treatment was discontinued.

After several months, I prevailed upon the patient to try the experiment of continuing the follicle and corpus luteum substances in the manner above outlined. The treatment presented less practical difficulty than usual, as the injections were given by the resident physician of the hospital with which the patient was associated. Again a dozen follicle substance injections were given, followed by six of corpus luteum extract. No result being obtained, a second series of follicle injections was advised, and here, almost as in the first case, menstruation appeared after one of these had been taken. The patient was encouraged by the fact that menstruation had thus appeared after a lapse of three

years, and was quite willing to keep up the experiments. One week after the flow, which was free and of four days' duration, the injections were again begun, and menstruation again ensued. This was repeated for four months, when the injections were discontinued. Amenorrhea for two months then occured, following which the injections were resumed, with the production of menstruation once more.

Skeptical though I have been about the value of organotherapy in menstrual disorder, this case appeared to leave little doubt as to the part which it played in this case. I do not know why an exactly similar plan failed in the other four cases in which it was tried. Three were of the so-called hypopituitary type, ovarian deficiency being presumably secondary. The other was a case of functional amenorrhea in a girl of nineteen, with no other discernable endocrin characteristics.

The encouraging result in the two cases above described is mentioned only casually, with no desire to vaunt this plan as a cure of amenorrhea. My own interest in it lies chiefly in the fact that such a method is in accord with what many of us believe is the true explanation of the mechanism of human menstruation, as I have already indicated. At any rate, it would seem worth while to try this method on a wider scale, rather than to draw our conclusions as to the value or lack of value of ovarian organotherapy from the administration of follicle substance alone or corpus luteum extracts alone.

So far as I have been able to judge, such effects as have appeared to follow the employment of the follicular hormone have been of a purely substitutional nature. In other words, no evidence has as yet been obtained to suggest that the substance actually awakens the slumbering ovarian mechanism to renewed activity. For example, in the case above noted, in which the administration of the follicular and corpus luteum substance was followed by the appearance of menstruation, the function failed to persist after withdrawal of the extracts. The same statement may be made with regard to the treatment, by this method, of the menopausal vasomotor symptoms, in so far as the subjective element will permit of conclusions. Whether or not this view is correct must be determined by the study of a far larger number of cases than have as yet been subjected to this form of treatment.

Amenorrhea of the endocrinopathic type is in itself a harm-

less condition, and is compatible with perfect health and well-being otherwise, so that the question which naturally arises with regard to the treatment of many of these cases is "cui bono?" It is hard to persuade women to submit to a long series of daily injections for the treatment of a symptom which, we must admit in all honesty, carries with it no known element of risk. There are two considerations which induce some women to submit to the treatment willingly, or even eagerly. The first of these is the psychic factor, the feeling on the part of some women that absence of the menstrual function defeminizes them and sets them apart from others of their sex. The other is the fact that amenorrhea of this type is most frequently, though not invariably, associated with sterility, so that the real motive for treatment in such cases is the desire for motherhood.

This is of course reason enough to justify efforts along the lines of rational organotherapy, and it is this incentive for treatment which I have most often encountered in the treatment of functional amenorrhea. I shall not here enter into a discussion of the endocrine factors, other than the ovarian, which may be concerned in the production of this type of amenorrhea, such as pituitary, the thyroid, etc. In all of them the amenorrhea is presumably due to a deficiency of the ovarian secretion as the immediate cause, whether this be primary or secondary, so that the ovarian therapy is certainly a rational portion of the treatment.

Where the desire for pregnancy does not exist, the motive for a long continued treatment, especially where this means frequent visits to a doctor's office for the injections, is lacking, and the enthusiasm of such patients is apt to wane long before that of the endocrine factors, other than the ovarian, which may be tical disadvantage of the treatment, although it should not deter us in our efforts to carry on these experimental studies on the human female on as large a scale as possible.

As to the effect of the follicle preparation upon the subjective symptoms of the menopause, either natural or artificial, I have been unable to convince myself as yet of any great superiority over the results of the older methods of organotherapy. While the number of cases of this sort which one encounters is naturally larger than those of the functional amenorrhea type, conclusions are hard to reach because of the difficulty of elimin-

ating the psychic factor, and because of the well-known fluctuations in the severity of the vasomotor symptoms exhibited from day to day by the same patient, as I have elsewhere discussed. The uncertainty of this form of therapy would, in fact, suggest that the characteristic vasomotor symptoms may be due to some factor, perhaps of sympathetic nerve mechanism, not attributable to the mere deficiency of the ovarian hormone or hormones.

SUMMARY

Recent investigations on various laboratory animals have tended to stress the importance of the follicle hormone and to minimize the importance of the corpus luteum factor in the oestrous cycle. This change in viewpoint appears to be justified by the available evidence, in so far as the lower animals are concerned.

An analysis of recent investigations upon monkeys, which menstruate much as do women, suggests that in these animals two types of sexual cycle may be observed. One is similar to that seen in the lower animals. It is dominated by the follicle, while the corpus luteum is apparently unimportant. In these cases menstruation may occur without ovulation, but the premenstrual changes in the endometrium are quite unlike those seen at a corresponding phase in the human. The hypertrophic changes are much less marked, and secretory changes are absent.

In the second type, the corpus luteum has the same chronological relation to menstruation as in woman. Ovulation occurs at about the same period, and the premenstrual endometrium is exactly like that in the human, including the secretory features.

In the human the evolution of the function appears to have advanced still further. Both histological and clinical evidence indicates that the prevailing type of menstrual mechanism is that in which the corpus luteum plays an important part, although the follicle is likewise important. Evidence is offered, however, to indicate that even in the human there may at times be observed a persistence of the more primitive follicular type of cycle. These cases constitute the exception and not the rule.

With regard to the therapeutic aspects of the subject, the view is expressed in this paper that the results in the laboratory animals are not applicable to the human patient, chiefly because of the differences in the mechanism of the sexual cycles.

The ovarian follicle hormone, as already indicated, is relatively less, and the corpus luteum, relatively more important in the human than in the lower animals, including monkeys.

Conditions of ovarian hypofunction, such as amenorrhea, furnish the logical indication for ovarian therapy. The employment of the follicular hormone in such cases has not as yet given very striking results, although this form of therapy is in its infancy. The suggestion is made in this paper that the menstrual mechanism be imitated by combining the administration of the follicle and the corpus luteum extracts in proper sequence. This will at least give a very rational basis for treatment, and, if potent extracts are available, will probably give better results than the use of follicle extract or corpus luteum extract alone.

The treatment of amenorrhea by this method is rational, but it presents several serious practical disadvantages. One of these is the difficulty of persuading patients to keep up, usually for a considerable time, a form of treatment necessitating at least daily hypodermic injections for considerable periods. The other is the fact that the condition treated is usually, so far as we know, in itself quite innocuous. The proportion of cases in which such methods of treatment are possible and proper is sufficiently great to yield a valuable human experimental material. While not so readily controllable as laboratory material, the results may prove just as valuable, especially if laboratory results be taken as the point of departure in their interpretation.

It is a pleasure to acknowledge my deep indebtedness to Dr. Carl Hartman, who has so cheerfully nurtured my desire to learn something of the reproductive cycle in the lower animals, and who has made many helpful suggestions in the preparation of this paper. To Dr. George W. Corner and Dr. Edgar Allen I am also under great obligation for their generosity in allowing me to read before publication their forthcoming papers dealing with this general subject.

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CORPUS LUTEUM IN ITS RELATION TO MENSTRUATION AND PREGNANCY*

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CORPUS LUTEUM AND PREGNANCY

The corpus luteum, as a gland of internal secretion, has aroused considerable interest for many years. This conception seemed so plausible, and appeared to be so well supported by experimental evidence, that for a long time it was quite generally accepted as a fact. On this basis many of the phenomena of the sexual cycle and pregnancy were explained. Further, it was responsible for the therapeutic use of various corpus luteum preparations, some of which at first appeared to give quite remarkable results. However, these have come to be almost entirely discredited, and along with this change the conception of the role of the structure as a gland of internal secretion has undergone considerable modification. In the brief space of this paper it is not possible to enumerate all these change, but it is desired to discuss some of the recent studies which show that certain modifications are necessary.

The hypothesis that the corpus luteum is a gland which produces an internal secretion was originated more than a quarter of a century ago. The basis for this assumption was that the histological appearance of the lutein cells, individually and collectively, closely resembled other glands known to produce an internal secretion. Such a hypothesis seemed very plausible, inasmuch as the theory had already been generally accepted that the ovary, as a whole, produces an internal secretion. The endocrine function of the corpus luteum was first proposed by Prenant (1), and soon thereafter appeared the extensive experimental work of Fraenkel (2).

Stimulated by the work of Sobotta (1896) on the origin and evolution of the corpus luteum in mammals, as well as the his-

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tological examination of completely developed corpora lutea, Prenant (1898) concluded that it is an organ by itself—a glandular organ. He suggested two hypotheses: First, it is a gland which puts into the circulation a product, or products which directly modifies the organism in its sexual activities and indirectly affects the entire organism; second, it suppresses ovulation, or renders it abortive, during gestation. Degeneration of the corpus luteum sometime before the end of pregnancy permits preparation for a new ovulation, the approach of which, by reflex action, is the cause of labor.

Fraenkel (2), at about the same time, sought to prove experimentally the hypothesis, suggested by Gustav Born, that the true corpus luteum of pregnancy, on account of its structure and process of development, must be a gland of internal secretion having the function of bringing about implantation and development of the fertilized egg. As a result of his experiments, he suggested further that the corpus luteum is responsible for the increased nutrition of the uterus during the reproductive years; also, for the increase in size and consistency of the uterus during this entire time, as well as the monthly cyclic hyperemia; and further, for implantation of the fertilized ovum and also for menstruation, if fertilization does not occur.

These attractive hypotheses have aroused a great deal of interest ever since they were first proposed. They are at least partly supported by clinical data and clinical observations subsequently collected. There exists quite a uniform conception concerning the anatomical structure of the corpus luteum. This includes the variations in morphology noted at the different stages of the sexual cycle.

At least twenty-five different functions have been attributed to this organ. Many of these already have been discarded, and, therefore, need not be mentioned. It is important to investigate further the relation of the corpus luteum to pregnancy. Many conceptions of this relationship as it pertains to the human are deductions from the results of animal experiments. Such conclusions are not entirely in accord with clinical observations.

Some diversity of opinion exists regarding the length of time the corpus luteum must function to insure implantation and development of the ovum in the uterus of animals. Not all animals are alike in this respect. Fraenkel (2) noted that cauteri-

zation of the corpora lutea in pregnant rabbits prevented implantation of the ovum, if performed during the first seven days after coitus, which act in this animal is necessary for ovulation. If cauterization was delayed until the seventh to the fifteenth day, pregnancy was interrupted.

In the dog and rat, Marshall and Jolly (3) found that removal of the ovaries or cauterization of the corpora lutea shortly after ovulation and fertilization prevented fixation of the ovum in the uterus. They also found that cauterization of all the corpora in these animals was practically equivalent to destroying the ovaries.

Loeb and Hesselburg (4) removed the corpora lutea of guinea pigs three to six days after copulation. They found that abortion had not occurred fourteen to eighteen days after copulation.

Robinson and Asdell (5) studied the relation of corpora lutea to the mammary gland in goats. They stated that removal of corpora lutea in pregnant goats always terminated pregnancy. Their method of extirpation is of interest. The corpus luteum was lifted out, following which the bed from which it was removed was curetted and then cauterized.

Mandl (6) in 1904 performed an interesting experiment. The left ovary of a rabbit was excised three days post-partum and post-coitus. This ovary was transplanted between the abdominal muscles. On October 5th three young rabbits were born alive. November 7th, coitus was repeated. November 9th, the right ovary was removed. November 21st the animal was killed and examined. Eighteen well developed ovular spaces were found in the right uterine horn. In the transplanted left ovary no corpus luteum was found. He concluded that, in the rabbit, implantation and further development of the ovum in the uterus does not require the presence of a corpus luteum.

Unanimity of opinion concerning the function of the corpus luteum in pregnant animals does not yet exist. The necessary requirements for a satisfactory experiment in animals can be fairly well controlled. Some conditions, however, have prevented attaining the ideal, for in most animals the corpora are multiple and comprise a relatively large proportion of the ovaries. If the corpus luteum is not completely removed it tends to regenerate quickly. The methods employed in most experiments, *i. e.*,

cauterization, or excision with cauterization, do not leave a normal ovary. There is some difficulty, therefore, in assuming that the results are entirely due to absence of the corpus.

Clinical data are even more difficult to obtain, for, obviously, similar experiments in the human subject cannot be deliberately planned. But certain necessary operations may contribute either directly or indirectly to the solution of this problem. The influence exerted on the pregnant uterus by removal of one or both ovaries has been of particular value. Oöphorectomy from the end of the second month of pregnancy to its termination has been reported so many times that it is generally accepted that the corpus luteum may be safely spared during this period. The importance of the corpus luteum in the first and second months is more cause for argument.

The importance of protecting the corpus luteum of pregnancy was emphasized by Oehsner (7). Instances were cited by him to show that almost any abdominal operation could be performed without interfering with pregnancy, providing the corpus luteum was not injured. Other operations were followed by abortion, which he considered to be due to the injury or removal of the corpus luteum. Many others support this impression; thus, Mackenzie (8) asserts, but without specific evidence, that removal of the corpus luteum during pregnancy results in abortion.

That abortion *may* occur following interference with the ovaries, no one will deny, but to say that it *will* occur is quite another matter. Ask-Upmark (9) has recently collected records of fifty-one oöphorectomies during the first two months of pregnancy. Seventeen of the women aborted following operation; however, of this number at least nine pregnancies were more or less complicated by other conditions, so that there is some doubt as to whether the operation itself brought about abortion.

Four of the fifty-one cases were of women in the first month of pregnancy. The first subject was operated upon September 6th, 1903. At this time both ovaries were removed. Pregnancy was not suspected during the operation. Just 269 days after the operation a full term child was born. Although the date of the last menstruation was not given, the report is so specific, as regards date of operation and delivery, that one cannot doubt that the corpus luteum and the ovaries were removed during the

first month. The presence of an accessory ovary is not probable, for the pelvic organs were all exposed at operation and, further, there was amenorrhea following delivery.

The second bilateral oöphorectomy was performed before the last menstruation was finished. Pregnancy was not suspected at the time of operation. A full term child was born.

The third bilateral oöphorectomy was accompanied by removal of the tubes on account of inflammation of the adnexæ. The operation occurred shortly after a menstrual period. Pregnancy was not diagnosed until one month after operation. Two hundred and seventy-six days after the operation a full-term child was born.

The fourth oöphorectomy was unilateral, but the corpus luteum was removed with the ovary twenty days after the last menstruation. No corpus luteum was found in the remaining ovary. The pregnancy was apparently progressing normally. The date of delivery was not given.

In addition to these reports from the literature, two somewhat similar cases are reported here:

Case 1: H. R., age 23, had been married six months. No pregnancies had occurred. Menstruation began at 13. It had never been regular, the intervals varying from twenty to thirty days. The flow lasts two or three days, with some pain during the first two.

Examination in July, 1926, showed a normal uterus and adnexæ. There was evidence of hypothyroidism which was thought to have some relation to the irregular menstruation. Thyroid extract was given by mouth. Menstruation occurred August 1st, 1926. Four weeks later a tender mass was noted in the left ovary. On August 31st, 1926, a laparotomy was done. The abdominal viscera were normal. In the pelvis was a normal uterus, slightly enlarged, but consistent with the size expected just before menstruation. The right ovary was normal and did not contain a corpus luteum. The left ovary was about the size of a hen's egg. It was removed. It contained one large cyst and a few smaller atretic follicles. On section the large cyst was seen to be filled with blood and a yellow, stringy material, which appeared to be lutein, containing cells. The lining of the cyst was yellow and velvety. Microscopic section through the large cyst showed the lining to be composed of large, light pink staining, luteal cells. There were also atretic follicles and corpora fibrosa.*

Subsequent to operation menstruation did not recur for, as was found later, pregnancy already existed at the time of operation. On May 7th, 1927, just 279 days after the last menstruation, a full-term

* Microphotographs were demonstrated by lantern slides.

child was born. Labor was normal and the patient was able to nurse the child normally.

The corpus luteum was larger than average, due to the increased amount of blood which it contained. It is obvious, however, that this was the only recent corpus luteum and that pregnancy continued without the proper corpus luteum after the thirtieth day succeeding the last menstruation.

Case 2 (mentioned in another paper, 10): Mrs. M. Mc., age 23, had been married five years. Her chief complaint was sterility. Three previous pregnancies all terminated at the seventh month. She was very desirious of having a normal, full-term child. General physical examination revealed nothing abnormal except in the pelvis. There was a deep bilateral laceration of the cervix with a retroversion of the uterus and slight descensus. The last menstruation occurred twenty days before operation. At the time of operation the cervix was repaired, the uterus suspended, and the appendix removed. Both ovaries were carefully examined and in the left one a large corpus luteum was found and removed. The raw area was covered over with sutures. This was the only corpus to be found in either ovary. A careful examination was made to determine this, for it is known that more than one corpus may be present at the same time.

Inasmuch as menstruation occurred just twenty days previous to operation, it was not considered that pregnancy could exist, for the appearance of the uterus gave no such indication. Therefore, it seemed perfectly safe to remove this corpus luteum for study. The particular interest at this time was to determine whether or not there was any hormone present in the corpora. This specimen was sent to Dr. Edgar Allen, who made sections and also extracted it to determine the amount of hormone present. It was found to contain more than 1.5 rat units. Microscopic examination showed a typical corpus luteum fully developed.*

Menstruation did not occur within the next two or three days, as was anticipated when the corpus luteum was removed. Later it became obvious that the patient was pregnant. The uterus enlarged consistently with the duration of pregnancy dating from the menstruation just preceding operation. Two hundred and seventy-two days after the last menstruation, a normal eight-pound baby was born. The course of pregnancy and delivery was normal in every way.

With reference to the last case, the objection may be raised that the corpus luteum was not all removed or that there was more than one true corpus luteum present, although only one was removed. In answer to these, it may be said that the corpus shelled out easily, leaving a clean surface. Sections made for microscopical examination showed that removal of the lutein cells

*Microphotograph of corpus luteum removed at operation was demonstrated on lantern slide.

was complete and that the capsule from the theca was also present. Whether or not there was another corpus luteum left in the ovaries is not so easy to prove. It is certain, however, that only a very small one could have been overlooked, and even that is very improbable, for careful search was made at the time of the operation because of interest in the relation of the corpus luteum to menstruation. The ovaries were both average size and were easy to examine. By comparison with many other similar ovaries it seems certain that no other corpus was present, except those associated with previous menstruation, and there is no reason to believe that such corpora are active.

Although corpora lutea are known to have been removed during the first month of pregnancy, it is still uncertain what relation this bears to the actual implantation of the ovum, for it is not known how long it takes the human ovum to reach the uterus One might infer from observation in animals that this period of transit is about three days. Such an inference, however, is only speculative.

The relation of ovulation to menstruation is just as fundamental to this problem as is the time of transit. Not all observers agree but there is much evidence to show that ovulation occurs about midway between two menstruations. Shroeder states that ovulation takes place about fourteen to sixteen days after the onset of menstruation. Shaw (11) confirms this, but gives a somewhat wider variation. Our own findings at operation have shown recently ruptured Graafian follicles from the twelfth to the eighteenth days, with the majority about the fourteenth or fifteenth day. While the most accurate method is actually to see a recently ruptured follicle, further evidence can be obtained by finding corpora lutea in a similar stage of development at a given interval after menstruation. Although Corner has recently stated that menstruation may occur in monkeys without ovulation, this is not the rule in women.

Evidence of the function of the corpus luteum in pregnancy is furnished in an indirect manner by the proceedure of De Lee (12), who transplanted a corpus luteum removed in one instance forty-two days and another, fifty-six days after the last menstruation. Abortion occurred shortly after operation in both of these cases. It is not certain that those grafts lived, but it has

been repeatedly shown that the corpus luteum may be successfully transplanted.

That pregnancy could occur without the presence of a corpus luteum in either ovary was supported by Abbott (13), who examined both ovaries of a pregnant woman without finding a corpus luteum in either.

CONCLUSIONS

With reference to the relation of the corpus luteum to pregnancy, it would seem to appear, during the latter months of pregnancy, that the successful development of the fetus in the human uterus does not require the presence of the corpus luteum, and there is considerable doubt as to its importance even for successful implantation of the ovum. The following reasons support this:

1. Many instances are reported in which the ovaries were removed during the latter months of pregnancy without any apparent disturbance.

2. Even in the first month of pregnancy the corpus luteum in at least five instances has been removed with the ovary without abortion occurring.

3. During the very time when implantation of the ovum is generally considered to occur, it has been removed without interfering with a successful implantation.

4. Once in the rabbit (Mandl, 6) and once in the human (Abbott, 13) pregnancy has occured without evidence of a corpus luteum in the ovary. The administration of preparations of corpus luteum in toxemias of pregnancy must be based on the assumption that a deficiency of corpus luteum exists. There seems to be no concrete evidence to support this assumption, for early removal of the gland has not been followed by toxemia.

5. The danger of abortion following an operation involving the corpus luteum has been exaggerated, for it is generally known that abortion may occur following any operation.

CORPUS LUTEUM IN RELATION TO MENSTRUATION

Irregularity in the interval, amount, or duration of menstruation is a problem with which the clinician is frequently confronted. Solution of such a problem requires a clear understanding of normal menstruation. As yet, however, all theories advanced in an effort to explain the cause for onset of menstruation are open to various criticisms.

It is generally accepted that the ovaries are responsible for periodic changes. This conception is supported by results of radiotherapy, for ovaries, which have been radiated, show complete, or partial, destruction of some of the epithelial elements, the changes varying in accordance with the dosage. If the larger follicles and corpora lutea are destroyed, with only atretic follicles remaining, the uterus maintains its development, but menstruation is delayed until mature follicles and corpora lutea are again formed.

Should the atretic follicles be excluded, the developing follicles and corpora lutea, singly or both together, remain to be considered as controlling factors. It is of interest, in this connection, to note that from follicles, corpus luteum, and placenta an identical hormone may be isolated, which, upon being injected into spayed animals, substitutes for all phases of oestrus. This hormone, when injected into women from whom both ovaries have been removed, has not yet produced a normal menstruation; it has, however, caused softening of the uterus and some enlargement, and in certain instances reproduced some of the subjective symptoms of menstruation.*

Primary amenorrhea, *i. e.*, failure of menstruation to appear up to the age of twenty or more, has not been relieved by injection of this hormone; however, in these individuals perceptible changes in the uterus have been noted. It is of interest to note that at operation corpora lutea were found in the ovaries of two of the subjects with primary amenorrhea. In one of these there was tuberculosis of the endometrium, but not all of the endometrium had been destroyed by the disease. In the other, the uterus appeared to be normal, and therefore was not removed; hence the condition of the endometrium is not known. Observation in still another individual in whom there was complete amenorrhea showed an apparently normal uterus with a corpus luteum in the ovary. The cause of amenorrhea in these three women has not been explained.

In a third group of patients, who had scanty and irregular menstruation, the results of injection of hormone have been more striking but have not been constant. Some of this group had symptoms of hypothyroidism and the administration of

* The hormone used for experiments was furnished by the experimental laboratories of Parke, Davis & Co. and of E. R. Squibb & Son.

thyroid extract alone has been more effective than use of the hormone. In other instances the hormone has produced better results than thyroid extract. The best results have been obtained by a combination of the two therapeutic agents when both hypothyroidism and hypoövarianism were present.

In earlier studies, it was considered that the small dosage might account for the meager results. This has not been substantiated by employment of larger amounts of the hormone, for with injection of the larger dose more of the hormone can be recovered from the urine, but neither is the menstrual flow increased, nor the irregularity of the interval improved. During the normal menstrual cycle, varying amounts of the hormone may be recovered from the urine. Results of quantitative tests of urine are not yet available. In addition to finding the hormone in urine, it is found in other body fluids. Frank (14) has shown that this hormone is present in the blood of normal women.

Since the hormone can be obtained from both the mature follicles and the corpus luteum, results obtained from study of the hormone do not help differentiate the importance of the two structures. In fact, it would lead to the conclusion that they have something in common. Perhaps the function started by the follicle is continued in the corpus. This might be expected since the lutein cells have their origin in the membrana granulosa.

Results obtained by extirpation of the corpus luteum in various phases of the menstrual cycle give some evidence as to the function of the corpus luteum. This procedure has been carried out many times by various observers. There is, however, no agreement as to the results obtained. This is difficult to explain, since the procedure is simple and the results should not be hard to interpret.

Fraenkel (2) cauterized follicles or corpora lutea in nine cases. He asserted that by removing the corpus luteum, or preventing its development, the next menstruation is delayed.

Corpora lutea and active follicles were removed in sixty-five cases by Ostreil (15). His method was excision of a wedge shaped piece of ovary containing the corpus and, if necessary, incision of the other ovary to ascertain the possible presence of a corpus luteum. In most instances when the excision occurred

during the first half of the menstrual interval, he found that the next menstruation occurred quite near the expected time, the delay being only one or two days. Excision from the 4th to the 21st day caused a delay of 14 to 28 days. Excision after the 21st day in most instances induced bleeding within two days.

Seitz and Wintz (16) found that in 11 of 12 cases removal of corpus luteum during the second half of the menstrual interval was followed by flowing on the second day, and that in 13 out of 15 cases the removal of large follicles during the first half of the interval induced menstruation within three and a half weeks.

In forty cases, Halban and Koehler (17) removed corpora lutea by incision and blunt dissection. In 92.5 percent of these, flow appeared from 2 to 4 days following operation and had a duration of 3 to 8 days. The duration and intensity corresponded to the normal menstrual type of the patient. When the next menstruation occurred it was usually at the regular interval after the induced menstruation and not the flow preceding operation.

In two of these cases in which the ovaries were removed the same phenomenon was noted as regards onset of flow, its occurrence being within two days and naturally followed by amenorrhea.

In thirty cases we have removed the corpus luteum from the ovary by method of incision and blunt dissection. Careful inspection has been made to insure complete removal. In most instances this is not difficult for the corpus luteum shells out of its bed, leaving a clean surface. In all but two of these cases removal of the corpus luteum was followed by an induced flow within forty-eight hours. In most instances the amount and duration of this flow closely corresponded to the normal average of the individual. It has not been possible in all instances to determine the onset of the succeeding menstruation, but, whenever this information was obtained, the interval between the induced flow and the next menstruation has been the average for that individual. In 11 instances the corpus luteum with the entire ovary in which it was contained has been removed. The results obtained were similar to the results following removal of the corpus luteum alone. In this series of forty-one cases, the results have been the same regardless of whether the corpus

luteum was removed during the first half or the second half of the menstrual period.

The influence of bilateral oöphorectomy has been observed in three instances. Two of these removals occurred during the first half of the intermenstrual interval. Induced flow appeared on the second day and simulated, both in amount and duration, a normal menstruation. The third bilateral oöphorectomy was done on the sixth day after the onset of menstruation. In this instance there was no induced flow. Our results in removal of the corpus luteum tend to confirm the findings of Halban and Koehler (17). Regardless of whether the corpus luteum was removed alone, or with the ovary in which it was contained, the flow, with two exceptions, was induced within two days. In one instance the appearance of the flow was delayed until the sixth day and in one of the bilateral oöphorectomies there was no flow at all following the operation.

Similar findings are reported by Ochsner (7), who in two instances removed the only remaining ovary. In one of these cases the previous menstruation had occurred ten days before operation and the induced flow began twelve hours after operation. In the other case the previous menstruation had occurred fifteen days before operation and the induced flow appeared about thirty hours after operation.

Summary and Discussion

Whether or not the flow induced by removal of a corpus luteum, represents a real menstruation is a question which can be satisfactorily answered only after making a histological examination of the tissues to determine the existing condition of the endometrium. In no case has it seemed indicated or justifiable to perform curettage to obtain material for such an examination. However, the question may be partly answered by two observations: first, the amount and duration of the induced flow is usually similar to the average menstruation for that individual; second, the succeeding menstruation usually occurs at the expected interval, reckoning from the time of the induced flow.

Discrepancy in the reported results following removal of corpora lutea may be explained by the difference in the method by which they were removed. Where cauterization is employed

the specimen is destroyed and no histological examination can be made. When this method is used diagnosis of the state of the corpus luteum can only be made from the gross appearance before it is removed from the ovary. A further objection to this method is that it is difficult to be certain when the whole corpus luteum is destroyed and whether the remainder of the ovary is not injured.

Excision of the corpus luteum is to be preferred; for this method permits inspection of the specimen at the time of removal as well as after it has been removed, and little or no damage is done to the remainder of the ovary.

The choice of method of removal is of considerable importance, for it is not always possible to determine the state of development of the corpus luteum without histological examination.

The possibility of substituting for the function of corpus luteum after its removal has been studied by Halban and Koehler (17). They transplanted the corpus luteum immediately after its removal in nine cases. The results of such a small series are not conclusive, but are suggestive that such substitution is possible. There is a further difficulty with their experiment, inherent in the fact that they produce no proof that the transplant survived.

Since a definite hormone may be extracted from the corpus luteum, it occurred to us that injection of this hormone immediately after excision of the corpus luteum might change the effect of removal. Injections were made as often as every eight hours, beginning within two hours after operation. As much as three hundred rat units were used, but the results were negative for the induced flow appeared at the usual time. It would seem from these results that there is probably more than one hormone concerned with menstruation.

It may be concluded that the corpus luteum is an important factor in controlling the menstrual cycle, but its exact role cannot yet be assigned. Whenever a corpus luteum is removed, either by itself or with the ovary in which it is contained, the next menstrual interval is disturbed. While observations reported in the literature do not entirely agree, the preponderance of evidence indicates that this disturbance is usually in the

nature of an earlier period, which establishes a new cycle of menstruation.

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CLINICAL MANIFESTATIONS OF WATER INTOXICATION IN A CASE OF SEVERE DIABETES INSIPIDUS, WITH SOME NOTES ON THE DISTURBANCES OF BLOOD COMPOSITION AND VASOMOTOR MECHANISM*

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In 1922, Weir, Larson and Rowntree described certain symptoms of water intoxication in a case of diabetes insipidus; the symptoms occurred after the administration of pituitary extract, the patient in the meantime taking water on request in the amounts to which he had become accustomed. In eight hours 5250 cc. of fluids was consumed, and 800 cc. of urine was passed; the nausea, vertigo, severe headache, and slight edema of the face and ankles resulted. Repetition of the experiment on the same and on another patient produced similar results. In 1923, Weir reported further studies on this peculiar form of intoxication and demonstrated a coincident increase in the relative volume of blood plasma. Rowntree conducted extensive experiments on the effect of the administration of excessive amounts of water to the experimental animal. He has produced ataxia, vomiting, and convulsions by this means, and Greene and Rowntree have demonstrated the fact that actual dilution of the blood may occur.

The relation of heat regulation to water metabolism has been studied by various investigators and its essentials have been reviewed by Barbour. Greene and Rowntree have recently demonstrated a decrease in body temperature in water intoxication and have shown that this result is largely independent of the temperature of the water used. Depression of body temperature may be produced by the ingestion of excessive amounts of water at body temperature and even by water up to 42°C.

* Read before the Association for the Study of Internal Secretions, Washington, D. C., May 17, 1927.

Rowntree has also mentioned the "heat liability" which patients with diabetes insipidus incur by taking large amounts of ice-water, and has noted the clinical symptoms such as shivering, weakness and tremor caused by this practice. He also noted that these symptoms may be relieved by the substitution of warm for cold water.

Since the physiologic factors involved in water metabolism and heat regulation are individually of such great importance, and particularly since their interrelation in the experimental animal has been demonstrated by the recent work of Greene and Rowntree, we have been interested in securing clinical data bearing on these points. An opportunity recently presented itself in the form of a patient suffering from severe diabetes insipidus secondary to epidemic encephalitis. The exceptionally severe character of his disorder, the presence of uncontrollable thirst, and the relative ineffectiveness of pituitrin in the control of the polyuria, made him a favorable if somewhat uncooperative subject. He presented symptoms and signs of water intoxication which furnished a fairly complete clinical counterpart of the syndrome of water intoxication observed in experimental animals; there was also evidence of a compensatory effort at heat regulation in consequence of the "heat liability" incurred by the ingestion of great quantities of ice-water. The case is reported because of its unusual interest from the standpoint of physiology and clinical medicine.

HISTORY OF THE CASE

A man, aged twenty-seven years, a railroad station agent, had been well prior to the onset of his present illness except for severe influenza in 1918. In March, 1923, weakness, diplopia, and easy fatigability were noted, and the patient, at the suggestion of his physician, drank rather large amounts of water. In November of that year he experienced a desire for water which he says was "not a real thirst"; the excessive intake of water soon amounted to six gallons (24 liters) a day, and a proportionate amount of urine was voided. During the following three years he worked at times but was weak, listless and, according to his family, increasingly inefficient. This gradual deterioration was substantiated by his gradual decline in the estimation of his employers; he had been removed from several positions and transferred in each instance to one carrying less responsi-

bility. His family had also noted a change in his personality, his disposition becoming morose and gloomy. The polydipsia and polyuria continued as before and at times were very severe; the patient mentioned that he had taken 15 gallons (60 liters) of water in a single day. In spite of an excessive appetite he had lost a good deal of weight. In June, 1926, following a period when weakness and lassitude had been particularly troublesome, he recalled the advice of his physician in regard to drinking water, and reasoned that if cold water was good for him, more and colder water might cure him. He therefore filled two buckets with cracked ice and consumed ice-water as rapidly as possible, drinking from one bucket as the other cooled. He recalls vomiting at this time, and finally had a convulsion while the bucket from which he was drinking was still in his hands. According to the patient's wife, the convulsion was epileptiform in type and was followed by deep coma. Recovery, however, was prompt, and the patient tried his ice-water treatment again with the same result, vomiting and convulsions. He had experienced six convulsions between June, 1926, and the following January, in each instance falling over with the bucket in his hands. The diagnosis of epilepsy seemed justified until the relation of drinking bouts to these convulsions was established.

The outstanding features on physical examination were those related to the encephalitic residue; the parkinsonian facies, slow clumsy muscular movements and coarse tremor were striking. The extremities were cold, dry and markedly cyanotic, and the patient was shivering constantly. The pupillary reactions and visual fields were normal and the ophthalmoscopic examination negative; the teeth were poorly kept, and the tonsils infected. There was no peripheral arteriosclerosis, the heart was normal, and the systolic blood pressure was 122, the diastolic 78. Respirations were often of a "grunting" type, and the patient coughed and cleared his throat repeatedly; the lungs, however, were clear. Abdominal examination revealed nothing of importance; the kidneys were not palpable. The deep reflexes were normally active and equal; there was no Babinski sign. The output of urine was 24,000 cc. in twenty-four hours; the urine was otherwise normal except for the specific gravity 1.001. The hemoglobin was 80 (Dare); erythrocytes numbered

5,000,000, and leukocytes 9,000; the differential count was normal. Blood and spinal-fluid Wassermann tests were negative. Roentgenograms of the skull and long bones did not show abnormalities. The blood urea was 14 mg., the total blood fats 284 mg., and the serum proteins 8.35 gm. for each 100 cc. of blood. Four readings of the metabolic rate, none of them entirely satisfactory because of involuntary muscular movements, averaged +30; this observation was of interest since in our experience practically all cases of secondary diabetes insipidus are associated with lowered basal metabolic rate.

Epidemic encephalitis, with the parkinsonian and respiratory syndromes, and secondary diabetes insipidus was diagnosed and the patient transferred to hospital for detailed study January 27, 1927.

For convenience and clarity in presentation, the course in the hospital will be considered from three standpoints: (1) the effect of pituitrin on polydipsia and polyuria; (2) the evidence pointing to water intoxication as a complicating factor, and (3) the "heat debt" and the mechanism of heat regulation.

EFFECT OF PITUITRIN

The effect of pituitary extract and the mechanism by which it controls the polydipsia and polyuria of diabetes insipidus have been under discussion since von den Velden and Farini and Ceccarino first described its antidiuretic effect. The mechanism by which this effect is exerted is still unknown, but the extract is active in controlling the symptoms in practically every case. In a large series of cases at the Mayo Clinic, only one other case has been observed in which the cardinal symptoms could not be effectually controlled by its use; this case also was secondary to epidemic encephalitis. In the present case, pituitrin controlled the polyuria only slightly; the polydipsia was apparently unaffected. The patient's thirst was apparently primary, and his case corresponded to the type discussed by Ebstein and others in which the primary occurrence of thirst was a feature. It seemed to be a sort of "compulsion" thirst, similar in nature to the compulsion hyperpnea observed in the respiratory syndromes associated with encephalitis. The extent to which the water balance was affected by this peculiar type of thirst, and the lack of effectiveness of pituitrin in its control is illustrated in Figure 1. The normal response of a

moderately severe case of diabetes insipidus is included for comparison.

WATER INTOXICATION

The untoward effects of excessive ingestion of water were first described by Miller and Williams. They noted vertigo, headache, and vomiting in cases of chronic nephritis in which large quantities of water had been ingested. The observations

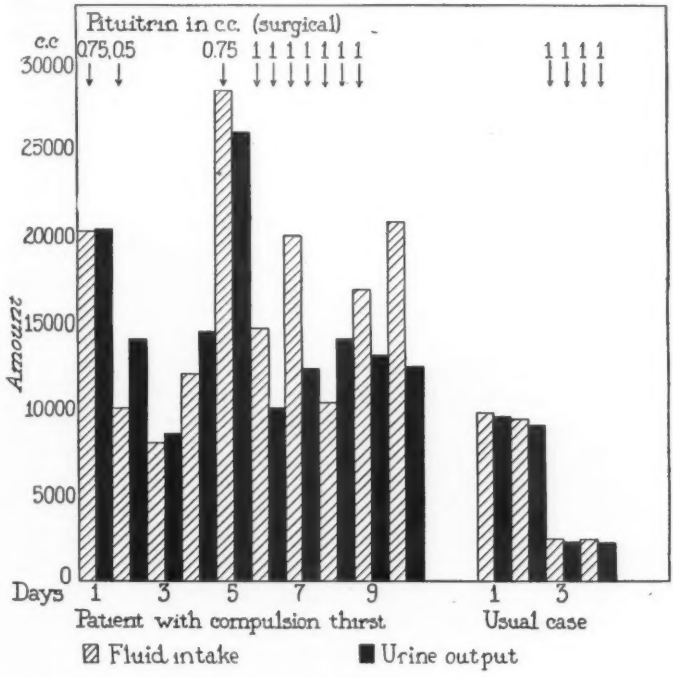

Figure 1. Pituitrin in diabetes insipidus.

of Weir, Larson and Rowntree have already been mentioned; they were the first to describe a condition of water intoxication in connection with diabetes insipidus, and also were the first to produce this condition experimentally. In their experimental work, pituitrin was given prior to the administration of water in order to decrease the output of urine. They postulated a disturbance of the salt and water equilibrium of the body as the

fundamental cause of the convulsions observed. Rowntree subsequently produced the condition in the experimental animal without the aid of pituitrin. In his animals, restlessness, asthenia, diarrhea, salivation, vomiting, tremor, ataxia, tonic and clonic convulsions, stupor, and coma occurred, and continuation of the excessive intake of fluid usually resulted in death. Greene and Rowntree have also demonstrated a dilution of the blood in these animals, as shown by a decrease in hemoglobin, serum protein, viscosity, electrical conductivity and molecular concentration. There was an increase in both the body weight and in the plasma volume. The content of chlorides and sodium and potassium in the serum was diminished out of proportion to the degree of dilution of the blood. The last mentioned observations have been confirmed by the work of Underhill and Salick.

The history of the convulsions in our case suggested that water intoxication and not epilepsy may have been responsible. While the patient was in the hospital, further evidence on this point was obtained. During the first three days of his stay, the intake of water fell greatly. This was due chiefly to our request that he take only what he needed to control his thirst. On the fourth day he disregarded advice and began to take water in greater quantities; on the fifth day the water exchange reached a level of 26,000 cc. On the sixth day 1 cc. of surgical pituitrin was given at 8 A.M. and at 5 P.M.; the intake exceeded the output by 4600 cc., and toward evening the patient was confused, tremulous, and very uncomfortable. He passed a fairly good night, but on the following day his desire for water was uncontrollable. One cubic centimeter of pituitrin (surgical) was given at 8 A.M. without effect on the thirst, and between this time and 5 P.M. he consumed about 16 liters of ice-water; at 5 P.M. he said he felt exactly as he did before the previous convulsions. He was restless, confused, and agitated, the face was flushed, and muscular movements poorly coördinated. There was slight ataxia, but no visible edema. He was put to bed at once and given 1.5 grains of phenobarbital; the intake of water was rigidly restricted. The following morning he felt much better and was able to control his thirst voluntarily on this day. There was a negative fluid balance of 4200 cc. in spite of two doses of surgical pituitrin of 1 cc. each. On the last two days of his stay in hospital, pituitrin was not given; the fluid balance

again became positive and the former symptoms of restlessness and confusion were apparent.*

The changes in the blood, the fluid balance, and the weight curve are summarized in Table 1. The complete picture of water intoxication in man has never been described, so far as we are aware, and we do not consider this case a perfect example. However, much clinical and laboratory evidence pointing to true water intoxication was obtained. The history of convulsions following the ingestion of great quantities of water is unique in our experience; while the encephalitis may have been partially responsible, water intoxication seems the more reasonable explanation. During a period when the patient was under our observation, he consumed 17,200 cc. of fluid in excess of the output of urine, gaining 9 pounds (7 per cent of the body weight), in four days; at the conclusion of this period toxic symptoms similar to those already described were noted. At this time there were also evidences of blood dilution, as shown by the reduction in the serum protein (13 per cent), the reduction in blood chlorides (20 per cent), and the decrease in blood sodium (27 per cent). The relative plasma volume, as shown by the hematocrit, was increased 8 per cent, and the whole blood volume, as measured by the method of Keith, Rowntree, and Geraghty, showed an increase of 4 per cent. (The latter reading is within the limits of error for this method.)

It has been shown by Weir that patients with diabetes insipidus present slight and somewhat inconstant evidences of blood dilution after the administration of pituitrin. We have had the opportunity to study one other case with reference particularly to the serum sodium and chloride. The data obtained from this case (Case 2), from Weir's cases (Cases 3 and 4), and from the case presented in this paper are compared in Table 2. It will be noted that in no other case did so great a decrease occur in the concentration of both electrolytes and serum protein.

The last reading obtained in our case (Table 1), deserves a word of explanation. The blood samples were taken during a period when the intake was about 5000 cc. in excess of the out put, although no very definite symptoms of toxicity were noted.

*A letter received recently stated that the patient has had no further convulsions and he has voluntarily restricted the intake of water.

TABLE I

Changes in the Blood During Different Phases of Water Intoxication (Case 1)

Date, 1927	Weight, pounds	Fluid		Pituitrin, surgical c.c.	Chlorine, mg. for each 100 c.c.	Sodium, mg. for each 100 c.c.	Osmometer reading, min. of water	Serum protein, gm. for each 100 c.c.	Plasma volume, c.c. for each kilogram	Whole blood, c.c. for each kilogram	Acid hematin hemoglobin, gm. per cent	Remarks
		Intake, c.c.	Output, c.c.									
1/27	132	21000	21050	0.75								
1/28	132¾	10000	14000	0.50	590							
1/29	132	8000	8500	None	670	395	51.2	8.35	60	107	16.8	
1/30	129	12000	14400	None								
1/31	129½	28400	26000	0.75		385	43.0	8.16				Relatively normal.
2/1	134½	14600	10000	2.00								
2/2	138¾	20000	12200	2.00	530	288	40.2	7.20	54	111		Phase of acute water intaxication.
2/3	141½	10200	14000	2.00								
2/4	121	16800	13000	1.00								
2/5		5200*	3100*	None	530	283	51.3	7.95	56	103	17.1	Mild symptoms of water intoxication.

*Six hours only.

TABLE II

COMPARISON OF CHANGES IN THE BLOOD IN VARIOUS CASES OF DIABETES INSIPIDUS

Author	Fluid		Pituitrin medication, c.c.	Hematocrit plasma, per cent	Serum protein, gm. for each 100 c.c.	Sodium chloride, mg. for each 100 c.c.	Sodium	Chloride	Remarks
	Intake, c.c.	Output, c.c.							
Weir, Case 4	6705	6407	None	62		600			
	2865	1942	1, obstetric	57		573			
			None	58	6.85	555			
			1, obstetric	71	6.25	551			
Weir, Case 3	5189	4525	None	67	7.31	648			
	3193	915	2, surgical	69	6.75	640			
	2380	1200	1, surgical	72	6.63	623			
	4732	4443	None	71	6.85	633			
Rowntree, Case 2	9750	9500	None						
	9250	9000	None		7.50		409	740	
	2500	2250	2, surgical						
	2500	2250	2, surgical		8.00		364	630	
Snell and Rowntree, Case 1	8000	8500	None	56	8.35		395	670	Relatively normal.
	20000	12200	2, surgical	59	7.20		288	530	Phase of water intoxication.
	5200*	3100*	None	55	8.00		283	530	Mild symptoms of water intoxication.

*Six hours only.

The values for electrolytes were slightly less than those obtained during the phase of water intoxication, whereas concentration of the serum protein and hemoglobin and the osmometer readings were about normal for this patient. A high concentration of serum protein and high osmometer readings characterized this case in all phases. It is probable that the electrolytes are the first elements of the blood to be disturbed by excessive intake of fluid, the proteins being influenced in a relatively slower manner and to less extent.

It has been shown in studies on water intoxication in the experimental animal that there is a decrease in serum protein of about 15 per cent and a reduction in electrolytes of about 25 per cent. This corresponds almost quantitatively to the changes observed in our patient; during the period of water in-

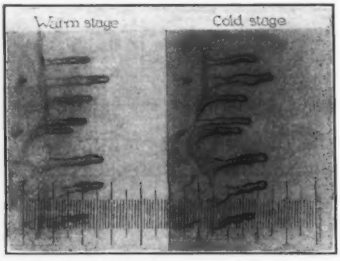

Figure 2. Nail-fold capillaries in diabetes insipidus.

toxication he also showed a greater fall in serum sodium and serum chloride than in any case of which we have a record. In conclusion, the enormous water balance, increase in weight and history of previous convulsions furnish additional support to the view that this was a case of true water intoxication.

DISTURBANCES OF HEAT REGULATION

The cold, cyanotic extremities and the constant shivering noted in this case were recognized as being due to a disturbance in the heat regulating mechanism. On his first day in the hospital a four-hour specimen of urine measured 5050 cc., a second four-hour specimen obtained after the administration of 0.75 cc. of surgical pituitrin amounted to 2000 cc. During this second period the hands became warm and pink, the shivering stopped abruptly, and the oral temperature rose to 99°F. He also per-

spired freely at this time. This remarkable occurrence prompted a further study of the heat debt which was incurred by the ingestion of large quantities of ice-water. The actual calorie debt in this case was calculated as varying from 315 to 1070 calories, depending on the amount and temperature of fluid taken, the average being about 660 calories. The food requirement was calculated as follows:

Basal requirement (1554 calories) + 30 per cent (elevation of basal metabolic rate) (466 calories)	=2020 calories
Specific dynamic action of food (10 per cent)	200 calories
Muscular exertion (20 per cent).....	400 calories
Average requirement for raising temperature of water	660 calories
Total	3280 calories

As a matter of fact the patient exhibited definite bulimia, reminiscent of Trousseau's celebrated case, and took food equivalent to about 4000 calories daily. The increased food requirement caused by the patient's heat debt probably produced a demand for food in excess of the amount actually required to raise the temperature of the ingested water. Such overcompensation might be expected and, if it occurs, would fully account for the excessive intake of food. Other factors which might be called into play to compensate for the heat debt in such cases are muscular movement and peripheral vasoconstriction. The former, as evidenced by shivering, was noted in this case, also about in proportion to the amount and temperature of water consumed. The vasomotor changes were studied in greater detail.

As has been previously stated, the reduction in water exchange effected by pituitrin caused a marked rise in the temperature of the body generally and a definite change in the color of the hands, from dusky and cyanotic to that of definite rubor. The nail-fold capillaries were studied in both phases on subsequent days. In the cold stage, the capillaries were dilated, with some cyanosis; the flow was slow and intermittent and a definite loss of tone was observed, the whole picture indicating arteriolar constriction. In the warm stage the capillaries were contracted, although loss of tone was still obvious. The flow was more rapid and homogeneous; cyanosis was not present in the capillary blood. These changes are represented in Figure 2.

The skin temperature was measured by the thermocouple. When the patient was taking ice-water freely, the temperature of the upper extremities was but little above that of the surrounding air. After the administration of pituitrin, during comparatively brief periods when thirst and polyuria were partially controlled, the temperature of the extremities rose from 5° to 15° Centigrade (Figs. 3 and 4). It must be remembered that these temperature readings are recorded during the period of one hour only, and consequently cannot be correlated accurately with the twenty-four hour output of urine. The hands were often warm and of good color after the morning dose of pituitrin, and cold and cyanotic by night. In general, the cold

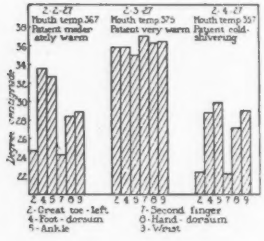

Figure 3. Surface temperatures in diabetes insipidus.

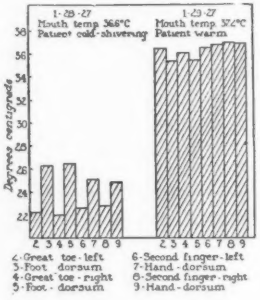

Figure 4. Surface temperatures in diabetes insipidus.

stage was less pronounced during periods of negative water balance, although it could be precipitated at almost any time by the patient, who was in the habit of taking three or four quarts of ice-water in a few minutes.

In order to obtain further evidence in regard to the elimination of heat in the extremities, studies were made with the Stewart-Kegerreis calorimeter. The heat production of the lower extremities is represented graphically in Figure 5; the lower reading was obtained January 31, the intake of fluid being 28,400 cc. and output 26,000 cc. on that day. The heat production a minute for each square inch of surface was 0.58 calorie, about comparable to that of a patient with advanced thrombo-angiitis obliterans or marked Raynaud's disease. The higher reading, which represents a normal heat elimination of 1.03 calories a

minute for each square inch of surface, was obtained February 30, the intake being 10,200 cc., and the output of fluid 14,000 cc. on that day. Here, as with the skin temperature, the negative water balance and relatively low intake of water after the administration of pituitrin seemed to accelerate the elimination of surface heat because of increased peripheral blood flow.

Calorimetric studies on the upper extremities gave a curious result, which is represented graphically in Figure 6. A normal curve of heat production in the hand is included for comparison. It will be seen that the hands tended to assume the temperature of the water in which they were placed; if warm when placed in the calorimeter, they produced a momentary rise of temperature, followed, after a short interval, by a fall. In this respect the upper extremities behaved as would those of a poikilothermic

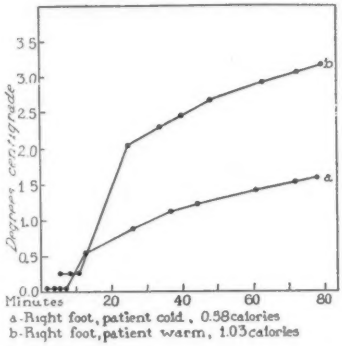

Figure 5. Calorimetric studies of the lower extremities in diabetes insipidus.

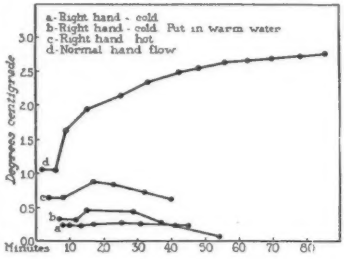

Figure 6. Calorimetric studies of the upper extremities in diabetes insipidus.

animal; the only curves of heat production comparable to these are those obtained in cases of Raynaud's disease. The gross appearance of the hands and the microscopic studies of the nail-fold capillaries also resemble the changes observed in Raynaud's disease. The underlying cause of the phenomenon in our patient was undoubtedly marked arteriolar spasm with capillary stagnation, and may be indicative of a compensatory mechanism to prevent the loss of heat from the body surface. The possibility that these disturbances of heat regulation may be due to water intoxication per se must be borne in mind for, as Greene and Rowntree have shown, this condition may cause a reduction in

body temperature. Our patient refused to tolerate an intake of warm water long enough for a detailed study of this point. Our previous experience with other patients suggests, however, that these vasomotor changes are due solely to the calorie requirements necessary to heat large quantities of cold water. The causal relationship of encephalitic changes to the vasomotor phenomena cannot be positively excluded, although a relation such as seen in this case has not, to our knowledge, been observed or described.

SUMMARY

In a case of severe diabetes insipidus secondary to epidemic encephalitis, the following unusual features have been observed:

1. A compulsion type of thirst relatively unaffected by pituitrin.

2. A history of convulsions, which on analysis appeared to be secondary to water intoxication.

3. Clinical evidence of such intoxication while the patient was under observation, accompanied by laboratory data suggesting blood dilution. These changes are similar in kind and degree to those accompanying experimental water intoxication.

4. A compensatory mechanism of heat regulation, to counterbalance the heat debt incurred by the ingestion of large amounts of ice-water. This mechanism included an increased intake of food to meet the excessive calorie requirements, muscular movements (shivering) and peripheral vasoconstriction producing phenomena similar to those observed in Raynaud's disease. These vasomotor changes appeared to be affected by pituitrin and the water balance at the moment.

The danger of pituitrin in such a case is obvious; with the kidneys rendered less active to an excess of water by the drug, the urinary output is reduced. Since the thirst was only slightly diminished, the possibility of blood dilution and consequent water intoxication is greatly increased.

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THE ACTION OF SUPRARENAL TISSUE UPON LECITHIN*

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Histological evidence suggests that the cortex of the suprarenal glands is closely associated with lipoid and cholesterol metabolism, although it is not yet certain whether the function of the glands is concerned with the synthesis, storage or breakdown of these substances. In regard to the lipoids, there is some evidence that both synthesis and breakdown may occur; cholesterin does not appear to be synthesised but to be taken up by the suprarenal cortex from the blood-stream.

It was found experimentally that the incubation of dried suprarenal tissue with lecithin in a saline medium at pH 7.4 and at 37°C. was always followed by certain changes. The concentration of the lecithin used was 0.5 gms per 100 cc. of solvent and that of the suprarenal tissue was 0.1 gms. The saline solvent contained 0.6% NaCl, 0.2% $NaHCO_3$ and 0.1% glucose. After all the components had been added, carbon dioxide was passed in with frequent shaking until pH 7.4 was reached. The flasks were then sealed and incubated at 37°C. after the addition of a little chloroform.

Within forty-eight hours the fluid containing the suprarenal substance became milky, while the control was not much altered. After three days there was a separation of the fluid into a fairly clear upper layer and a markedly milky lower layer, while at this time a slight milkiness was developing in the control without any separation of the fluid into layers. This suggests that the presence of suprarenal tissue has accelerated a hydrolysis of the lecithin which was proceeding more slowly in the alkaline control fluid.

Using equal parts of lecithin and cholesterol these changes became more distinct. After four days' incubation the cholesterin in the control flask had come out of suspension as a white

* This work was carried out under the Foulerton Committee of the Royal Society.

crystalline mass at the bottom of the flask. In the flask containing the suprarenal tissue the fluid was sharply divided into two layers, and at the bottom of the flask was an oily paste without crystalline structure and consisting largely of cholesteryl esters. Other gland substances tested in a similar manner were thyroid, parathyroid, anterior and posterior pituitary and thymus. Of these none produced the characteristic milkiness of the solution within forty-eight hours, while in four days the thymus alone appeared to have any pronounced action. It therefore seems probable that one function of the suprarenal gland is to hydrolyse lecithin and that the resulting fatty acids combine with cholesterol to form esters.

The hydrolysis of lecithin should lead theoretically to the liberation of choline, and the changes which have been described should be roughly indicated by the weight of choline mercurichloride recovered from the solutions. From the formula usually given, one gramme of lecithin should contain 156 mgm. of choline. As will be shown later, during the long period of incubation choline tends to be converted to some other substance, perhaps betaine or neurine, which gives considerably less than the theoretical yield of choline mercurichloride. After complete hydrolysis, one gramme of lecithin should yield about 780 mgm. of betaine mercurichloride. One would in any case expect a larger yield of mercurichloride from the fluid containing the suprarenal substance than from the control, and this was found to be the case:

Substrate	Mgm. Mercurichloride per 100 cc.	
	Control	Suprarenal
Lechithin only	21.2	44.0, 41.2
Lecithin and cholesterol	51	68.5, 79.6

In both cases the test fluid yielded more of the choline derivative than the control. It is also seen that the addition of cholesterol accelerated the rate of hydrolysis of the lecithin about equally in both solutions, so far as is indicated by the mercurichloride precipitate. The other gland substances mentioned above gave figures sufficiently near those of the control to suggest again that by comparison their action upon lecithin is comparatively slight.

It is noted, however, that although suprarenal substance appeared to accelerate the hydrolysis of lecithin, the yield of

mercurichloride was only about ten per cent of the theoretical. It seemed possible that the gland substance might have some action upon the choline so that its combination with mercuric chloride was prevented.

On incubating choline hydrochloride with suprarenal substance, it was found that a considerable reduction occurred in the amount of mercurichloride recovered from the test fluid, as compared with that recovered from the control. Incubation was carried out in the saline medium already described for four days at 37°C and pH 7.0. The fluid was then filtered, acidified, evaporated almost to dryness and extracted with alcohol. To the alcoholic extract a saturated solution of mercuric chloride in alcohol was added, and after standing the precipitate was filtered off, dried and weighed.

Theoretically one part of choline should form nearly fifteen times its weight of choline mercurichloride, and since the concentration of choline hydrochloride used was 20 mgm. per 100 cc. of solvent, the theoretical yield from the control should have been about 300 mgm. of choline mercurichloride. Assuming that a conversion to betaine occurs during incubation, then the yield would be about 100 mgm. per 100 cc. of fluid. The yield from the control flasks was usually of this order, but when suprarenal substance was present, it was always considerably less.

Mgm. Mercurichloride Recovered per 100 cc.		Gms. Suprarenal Substance Used per 100 cc.
Control	Suprarenal	
95	21	0.1
105	25	0.1
90	36.5	0.1
86	12	0.2
127	54	0.1 (ether extracted)

In the last instance the suprarenal substance had been extracted for a week with ether in a Soxhlet apparatus.

Although the method of recovery of the mercurichloride precipitate is admittedly a rough one, it indicates definitely that the presence of suprarenal substance has caused a decrease in the amount of the precipitate as compared with the control fluid.

On distilling the fluid in which suprarenal substance had been incubated with choline hydrochloride, formic acid was pres-

ent in the distillate in readily appreciable amounts. Oxalic acid did not appear to be present in the fluid.

On evaporating the fluid to dryness, extracting with alcohol and boiling with cyanamide, positive colour tests for creatinine were obtained after the necessary treatment with hydrochloric acid.

COMMENT

If choline hydrochloride is warmed in alkaline solution in the presence of an oxidising agent, trimethylamine is given off and oxalic acid is formed. If formic acid is to be produced through this type of reaction, it must be formed by a separation of the carbon atoms of the glycol group, a reaction which does not appear probable.

On the other hand, it is possible to conceive that the formic acid is produced by a process of demethylation of the nitrogen atom of the choline, leaving the glycol group intact. This would account both for the diminuation of the mercurichloride precipitate, and also for the appearance of the formic acid. Although demethylation is considered to be a rare biological event, it is not unknown. It has been shown to occur in the case of the trimethyl- and dimethyl-purines, and it has been suggested by Riesser (1) as occurring in the formation of creatine through the condensation of choline and urea. It must also occur in the formation of guanidine from choline, as suggested by Paton (2). Further, Clément (3) has identified formic acid in the suprarenal glands.

Boruttau (4) suggested that the side-chain of the adrenaline molecule might be part of a choline nucleus, and if demethylation of choline occurs it is conceivable that methylaminoethanol will be a stage in its breakdown. In its aldehyde form this substance may combine with pyrocatechol:

$$(CH_3)NH.CH_2CHO + C_6H_4(OH)_2 \rightarrow C_6H_3(OH)_2CHOH.CH_2.NH(CH_3)$$

to form adrenalin, as formaldehyde is known to combine with phenol in alkaline solution:

$$H.CHO + C_6H_5(OH) \rightarrow C_6H_4(OH).CH_2OH.$$

While it is admitted that the evidence for the formation of adrenalin from choline and pyrocatechol is slight, the chemical changes involved are simple, being those of oxidation and condensation as compared with the rather complex changes necessary

to transform tyrosine to adrenalin, a view which though generally accepted, has no experimental foundation. The present view is supported by the histological evidence of lipoid degradation, and since aminoethanol, the base of cephalin, can also be theoretically derived from choline, the occurrence of lipoid synthesis in the suprarenals may be accounted for. Finally it is known that the disappearance of lipoid granules from the cortex is accompanied by cessation of adrenalin output.

SUMMARY

1. Suprarenal gland substance causes a lipolysis of lecithin. In the presence of cholesterol this reaction is accelerated and cholesteryl esters are formed.
2. Suprarenal substance appears to attack choline. Formic acid is found in the distillate.
3. It is suggested that the side-chain of the adrenalin molecule may be derived from choline.

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VERTIGO AND DEAFNESS ASSOCIATED WITH HYPOTHYROIDISM*†

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DETROIT

The association of deafness with hypothyroidism is fairly well known and this is particularly true of cretinism, where the incidence of deafness is remarkably high. It is not surprising, therefore, that we find symptoms referable to the semicircular canals and organ of hearing associated with hypothyroidism in adults. We have encountered many cases characterized by noises in the ear, attacks of dizziness which may be associated with vomiting and loss of consciousness, and progressive loss of hearing in patients suffering from hypothyroidism.

The following case illustrates the type we have encountered:

A woman of 36 complained that for one and a half years she has had spells of vertigo of such severity that objects would seem to spin around. Nausea and vomiting invariably accompanied the attacks, which usually lasted about one hour. They came at intervals of one to two weeks. It was necessary to lie down at the onset of the attack. The attack gradually wore off during the course of an hour, but during the intervals there was a constant buzzing and hissing in the right ear. She had lost the hearing of the right ear during the course of one and a half years. She tired easily.

The following findings in the physical examination were of importance: She was a woman of normal weight for her height of five feet four inches. She was totally deaf in the right ear. There was no other cranial nerve involvement. The thyroid gland was palpable. The skin was dry and she did not sweat very much even in hot weather. The extremities were cold. The nails were brittle. The basal metabolism was minus 28 per cent. The Barany test gave no reaction in the right ear. Blood pressure was 126/60. Other laboratory findings and roentgenological studies of the mastoid were normal.

She was placed on half a grain of desiccated thyroid extract three times a day and after two weeks noticed an improvement in her condition. She continued on this medication for four weeks until her basal metabolism was normal. Since that time she has taken smaller doses intermittently and has had no attacks during a course

*From the clinic of Drs. Ballin, Allen and Moehlig.

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of nine months. She has no more dizziness, except mild attacks of vertigo. The deafness, of course, is uninfluenced.

The numerous etiological factors mentioned as producing Meniere's syndrome will not be discussed in this paper. I have encountered twenty-four cases of vertigo and deafness in patients with low metabolic rates. Of particular interest, as having a direct bearing upon the etiology, is the fact that some of our subjects had had partial thyroidectomy for toxic goiter, including the adenomatous and exophthalmic types, followed within a short time after operation by symptoms of hypothyroidism with a low basal metabolism. The incidence of hypothyroidism in these operative cases has been much higher since the operation for toxic goiter has become more radical. Alexander (1) in a recent three volume work devoted to neurology of the ear gives but brief mention of post-operative myxedema and ear noises. All operative cases developing vertigo had metabolic rates varying from twenty-five to sixty per cent above normal previous to operation, contrasting rather strikingly with a post-operative minus rate of eighteen to forty per cent.

The sex incidence in our series was sixteen females and eight males. The majority of non-operative cases in the female were around the menopause age.

As to the pathological changes present, we have had no opportunity to study the auditory organs of any of our cases. There are varying and diverse reports of the structural disorders found in the auditory organs in cretinism and myxedema. Otospongiosis and otosclerosis are reported by some. The reports from the otologists who studied our cases were that the patients suffered from nerve deafness and that they had a delayed response to stimuli in the affected ear.

The duration of symptoms ranged from two months to six years, the shortest duration being in those individuals in whom we recognized the symptoms soon after operation, and in those who had come to us since our attention was called to this type of association. The attacks would come on at intervals of one to two weeks and would make the individual intensely sick; vomiting usually accompanied the attack. At times fainting would also occur and it invaribly caused such intense vertigo that support was necessary. The duration of the attacks was from a few minutes to two hours. Buzzing, ringing in the affected

ear, described frequently as like hissing steam, was constantly present between attacks. We never found that both ears were involved.

It was surprising to note that despite the very low basal metabolism but few cases showed any striking hypothyroid signs. We consider this important because, for this reason, the association is not thought of. Dryness of the skin, lethargy, lack of memory, fatigue and cold extremities were the usual complaints in the severer grades of hypothyroidism. There was no marked obesity in any of our cases, but in some of the surgical cases the gain in weight after operation was quite rapid, though not excessive.

All the patients had either a normal or subnormal blood pressure. Some of the operative cases had had high blood pressure previous to, but were normal or subnormal after operation.

Laboratory findings, other than the low metabolism, were normal. The x-ray findings of the mastoids were also negative. The Barany test gave no reaction on the affected side in those cases which had gone on to total deafness. There was no other cranial nerve involvement.

Barlow (2) in studying the vestibular nerve function in fifteen cases of myxedema concludes that there is a definite clinical vestibular picture which can be demonstrated by the equilibration tests and is in the nature of a delayed response to stimuli; furthermore, that there is no relationship between the basal metabolic rate and the degree of this retardation.

In one case in which he was able to test the effect of thyroid therapy, improvement in response to stimuli was noted, and suggests the possibility that this clinical picture may be improved by thyroid extract. The improvement noted in hearing in eighteen of our cases which had not gone on to total deafness would bear out Barlow's suggestion.

Treatment consisted of desiccated thyroid extract in sufficient dosage to bring the basal metabolism to normal, and then the dosage was reduced to maintain the normal. Marked improvement was noted in the vertigo symptoms and practically all had but very mild attacks following this form of treatment. Spells of vertigo were present occasionally. The deafness was, of course, not improved, but I am led to believe that in some of the early cases we have prevented the development of deaf-

ness. The benefit derived from the thyroid extract was so marked that there hardly seems to be any question as to its efficacy. Outstanding is one case—that of a nurse with symptoms of one and a half years' duration. Her symptoms were very suggestive of a cerebello-pontile tumor. She showed immediate improvement on one-half grain (0.33 mgm.) of desiccated thyoid t. i. d. She continued this for three weeks and for seven months has been taking it sporadically. Some of the cases with very low rates have been taking it continuously.

Some of the conditions with which this syndrome may be confused are cerebello-pontile tumors, migraine, labyrinthitis, and syphilis. In the tumor cases, differentiation of a well developed case should offer no trouble, as there are present headache, choked discs (missing at times, of course), nystagmus and involvement of other cranial nerves. The basal metabolism is not affected. In early cases confusion is quite possible, but the therapeutic test is also helpful.

Differentiation from migraine offers less difficulty. While migraine symptoms are similar to the syndrome mentioned, nevertheless there is present headache, which the individuals afflicted with this vertigo do not usually have. Likewise, there is no difficulty in the hearing, nor is there any disturbance in the basal metabolism and a familial tendency is often present.

Given a case of vertigo, with or without vomiting or fainting spells, ringing and buzzing in the ear, lessened or absent hearing, low or normal blood pressure, and a low metabolic rate, in the absence of striking hypothyroid signs, we are justified in the conclusion that we are dealing with a unique and characteristic symptom complex heretofore not appreciated as a clinical entity, and that the exhibition of thyroid in these cases may be expected to result in marked relief or complete cure.

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THE EFFECT OF PREGNANCY AND LACTATION ON THE BLOOD CALCIUM OF THYRO-PARATHYROIDECTOMIZED DOGS

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In our previous work (Fisher and Larson, 1925) we have shown that a decrease in the calcium of the blood serum invariably accompanies the onset of tetany in a thyro-parathyroidectomized dog. The work of MacCallum and Voegtlin (1909), Salvesen (1923) and Hanson (1924) was not entirely accepted by Dragstedt, et al. (1924).

The methods used in preparing potent parathyroid extracts and in operating upon the dogs were those reported in a previous paper (Fisher and Larson, 1925). The dogs were purposely kept on a meat diet. The calcium values are all of the blood serum and are given in terms of 100 c.c. of blood serum. All determinations were made in duplicate by the method of Clark and Collip (1925).

Protocol, Dog A. Female Collie. Weight, 13 kgm.
March 12, 1925—Thyro-parathyroidectomy performed.
March 15-22—Markedly depressed.
March 25—Appetite fair. Condition good.
March 26—9 p. m. Tetany. 5 cc. extract given.
March 27—Ate greedily. Placed in pen with other dogs.
May 6—Removed from general pen.
May 7—Gave birth to 5 pups.
June 9—Blood calcium. 8.22 mgm.
June 18—Blood calcium. 7.56 mgm.
July 9—Blood calcium. 10.80 mgm. Weaned pups.
July 9, 1925, to August 19, 1926—Condition good. The blood calcium values varied from 9.5 to 11.08 mgm. Twelve samples were analyzed at regular intervals during this period. At the end of this period a careful autopsy was performed but no parathyroid tissue was found.

Protocol, Dog B. Female Shepherd. Weight, 14 kgm.

June 13, 1925—Thyro-parathyroidectomized.

June 15—Impending tetany. 6 cc. extract injected.

June 16—Severe tetany. 8 cc. extract injected.

June 19—Severe tetany. 10 cc. extract given. Complete recovery.

July 8, 1925, to January 28, 1926—Ten blood calciums at regular intervals varied between 9.28 and 11.05 mgm.

March 27, 1926—Animal pregnant, near term. Blood calcium 7.22 mgm. Some evidences of tetany such as hyperpnoea, but no injection was made.

March 30—Blood calcium 7.69 mgm.

March 31—Blood calcium 8.40 mgm. Gave birth to 9 live pups.

April 2—Blood calcium 9.70 mgm.

April 3 to May 21—During this period 5 blood calcium determinations varied between 9.55 and 10.25 mgm.

July 23—Refused food.

July 24, 1926—8 a. m. Animal dead. Body heat present.

Autopsy. Important findings. Mass of hair 10 cm. in diameter in pyloric end of the stomach. Broncho-pneumonia in middle and lower lobes of the right lung. Two glands in the neck region, the one located on the right side at the level of the cricoid cartilage 1 cm. in diameter, the other 2mm. in diameter in the midline of the neck, midway between the cricoid cartilage and the upper border of the manubrium sterni.

Microscopic examination. The larger gland was lymphoid tissue. The smaller gland was parathyroid tissue.

DISCUSSION

From the data presented it is evident that there is a decrease in blood serum calcium during pregnancy and lactation. In the case of Dog A the calcium analyses were not made until nearly a month after the birth of the pups. Even at this time, which was near the end of the lactation period, the calcium was near the tetany level. Within a month after the pups were weaned the calcium returned to a normal level. In the case of Dog B, in which the calcium of the blood was determined at more frequent intervals, it was shown that the calcium decreased gradually, almost to the tetany level as pregnancy advanced. There was a rapid return to normal following delivery.

These results suggest that during lactation and pregnancy such demands are made on the calcium supply of the body that the blood calcium level is markedly changed even in the presence

of at least one accessory parathyroid gland. Hanson (1924) has shown that it is possible to produce tetany in pregnant bitches by removal of only the external parathyroids.

These results are not in agreement with those of Dragstedt, et al. (1924). The analyses reported by this investigator vary from 9.3 to 10.4 mgm. per 100 c.c. of blood. These values are within normal limits for blood serum. It is not stated whether the values are of the serum or whole blood. The method used (Clark, 1921) is applicable to whole blood, serum or plasma. For whole blood the values are much too high. However, values like 9.3 mgm. per 100 c.c. in the case of a dog dying in tetany are inconsistent with the findings of Collip (1925) and Fisher and Larson (1925), where an improved method for calcium determination was employed.

Both of our animals showed that during pregnancy and lactation there was a marked decrease in the calcium of the blood serum in spite of the fact that some parathyroid tissue was found at autopsy in the one dog. We believe there was accessory parathyroid tissue in Dog A. These dogs did not experience many severe attacks of tetany, even though they were fed on a meat diet. The tetany was easily controlled, and in a short time parathyroid extract was not necessary. The calcium level returned to normal and remained constant. The superposing of pregnancy and lactation on the condition of parathyroid deficiency, when the animals were on a meat diet, caused a marked decrease in the blood calcium level. When the demands on the calcium were removed, there was a return of the blood calcium to normal.

SUMMARY

In two cases it was shown that pregnancy and lactation were accompanied by a decrease in the blood calcium of thyroidectomized and partially parathyroidectomized dogs that had maintained a normal calcium level preceding pregnancy.

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A CASE OF RETINITIS PIGMENTOSA ARRESTED BY ORGANOTHERAPY AND ANTISYPHILITIC TREATMENT*

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The term "retinitis pigmentosa" is misleading, but since it has been long in use it is employed in this communication. De Schweinitz's suggested designation, "pigmentary degeneration" of the retina, might be better. Collin's and Wilmer's term, "retinal abiotrophy," is more descriptive. In view of the grave disposition in this disorder to total and permanent blindness, it is believed that a preliminary report of an arrested and improved case will be of interest, especially since an older brother and sister of the patient are in the school for the blind, from the same cause. These are all quite typical cases with abiotic degeneration of the retina, the thread-like contraction of the blood vessels, pigment deposits, increasing contraction of the visual field, and progressive blindness. The particular interesting thing about the case reported, especially as to diagnosis, is that the sella turcica was seen to change radically under observation, clearly showing pituitary disease.

Consanguinity is a feature, though rather remote, the great grandparents on the father's side having been first cousins. There is no history of impaired vision on either side of the family. No history of syphilis can be traced and the Wassermann reaction is negative.

The patient was extremely small at birth. The mother's father had heart disease that might have been syphilitic. The mother's brother had a child afflicted with "glandular trouble," but who got well. The father's brother had a son born physically defective and not walking until three years of age. Syphilis

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crept into the blood somewhere down the line. We are convinced from our experience in numerous cases of eye disease that a negative Wassermann test should be disregarded. From a large experience in diseases of the eye, we are compelled to conclude that inherited syphilis is at the bottom of many of these cases, even though the indications may be negative. This disease seems to have special affinity for the pituitary body, the structures about the third ventricle, and for the eye, as well as the other structures coming from the ectoderm. We are convinced that there is a syphilitic blood state of great importance indeterminable by present laboratory methods.

It should be said that while the cases herein mentioned were all typical, there was but slight nystagmus, no strabismus, nor any mental deficiency. The three children are all very bright and are making high marks in school. The first two cases are reported for comparison and to show the familial tendency. There are no other children in the family. Our information concerning these two children is rather limited, except as to the present state.

CASE I. W. J. C., aged eighteen, male. There is no history of serious infectious disease or important illness of any kind. Development was normal and he is now physically sound. Impairment of vision began at six. A skiagram made on July 22, 1922, revealed the sella turcica to be of the deep saddle type with clinoid processes closed and pressing upon the pituitary body. Progressive blindness compelled him to begin residence in a school for the blind at twelve. No glandular or syphilitic basis was recognized nor was much treatment given since the case was believed to be hopeless.

CASE II. E. M. C., aged fifteen, female. The history of this patient is quite similar to that of the older brother. She gave no history of infection or serious illness. Her development was normal. Mentally she is very bright. Trouble with the vision began at eight and progressed steadily. She entered a school for the blind at fourteen. July 22, 1922, x-ray examination revealed a sella turcica of the dish type with over-development, clubbing and closing of the posterior clinoid processes, with great pressure. Possible syphilitic inheritance and pituitary basis of the trouble was not considered. No special effort was made in treatment, as it was thought nothing helpful could be done.

CASE III. R. A. C., aged nine, male. The patient weighed four pounds at birth and developed slowly. Mentally he is very keen and is making high grades at school. A series of important infectious diseases occurred, including a severe attack of influenza at six and pneumonia and scarlet fever with nephritis later. There has been no

post-nasal bleeding, epileptoid spells, or vomiting; no polyuria, nystagmus, strabismus or diplopia; no pain, no night blindness. X-ray examination (Richardson) made as a precaution at six, July 22, 1922, showed a normal sella turcica. At this time the health was good. Three years later vision was impaired and the sella was found decidedly abnormal. After two months, September 15, 1925, when vision was much worse, another picture showed marked clubbing of both clinoid processes with serious encroachment on the pituitary body.

Examination showed the patient to be undersized and unhealthy in appearance, poorly nourished with flabby muscles, thin and anemic looking. The blood pressure was 70/50. The blood examination showed: Hemoglobin, 65 per cent; red blood cells, 4,000,000; leucocytes, 7,800. A differential count showed: polymorphonuclear leucocytes, 53 per cent; lymphocytes and mononuclear cells, 36 per cent. The phenolsulphonpthalein test gave 75 per cent recovered in two hours. The alveolar air test gave 25 mm. The bones were small, the hands narrow and tapering and the skin very smooth and dry—all suggestive of pituitary insufficiency. The adrenal white line was a prominent feature. Bust, hips and legs were decidedly of the feminine type. The sex organs were not properly developed. The biceps, epigrastric, umbilical, cremasteric, and knee reflexes were all greatly exaggerated, which would seem to be unusual. Examination of the urine showed absence of sugar, albumen, casts, and red blood cells. No evidence of focal infection was found; x-ray examination showed the sinuses to be clear. A calcium deficiency was indicated by a tendency to marked kyphosis. The color vision was apparently normal, except for some doubt about green. Vision was 5/200 minus.

It was suspected that there was a syphilitic inheritance at the basis of the condition, and it was certain there was pituitary disease. The patient, accordingly, was put on glandular therapy, chiefly pituitary, but including adrenal and thyroid, according to indications, together with the old mixed treatment for syphilis, namely, mercury, iodide, nux vomica, and iron. A full vitamine diet was prescribed. The improvement was prompt and marked.

After six months' treatment, the patient had grown two inches, had gained nine pounds in weight and the general condition was excellent. The blood pressure was up to normal, 95/60. The hemoglobin was 82 per cent; the red blood cells, 4,500,000; the leucocytes, 7,200. The differential count showed polymorphonuclear leucocytes 66 per cent and lymphocytes and mononuclear cells 34 per cent. The "Pthalein" test gave 95 per cent recovery. The alveolar air had increased to 40 mm. The kyphosis was much corrected and the endocrine func-

tions seemed much better. The patient was now developing rapidly and was in fine condition mentally and physically.

At this time the retention in vision was surprising: the retina had cleared very much; the spots had faded perceptibly and scar tissue appeared to have taken the place of the pigmentary deposits. Unquestionably the condition of the eye grounds was materially better, indicating that the disease was probably arrested.

It is sufficient in concluding this report two years later, to say that the improvement of vision has been maintained and is now 12/200.

Abstract Department

Importance of creatine, creatinine, and arginine in adrenalin action (Uber die Bedeutung des Kreatins, des Kreatinins und des Arginins für den motorischen Effekt des Adrenalins). Brodd (C. A.), Skand. Arch. f. Physiol. (Leipz.), 1927, **50**, 97-154; Abst. Physiol. Absts., **12**, 116.

In perfusion of the blood vessels of the eviscerated frog by Göthlin's fluid, creatine in a concentration of 0.001% increases the flow, but in this or less dilution enhances the constrictor action of adrenalin. Creatinine in 0.05% solution dilates the vessels, but does not influence adrenalin action, while arginine in 0.0003% solution facilitates adrenalin constriction. Neither creatine, creatinine, nor arginine has any action alone on the rabbit's uterus, and of these only arginine appears to facilitate the effect of adrenalin on the uterus.

Experimental research on the influence of adrenal cortex on body growth. Castaldi (L.), Rev. sud-americana endocrinol. immunol. quimioterap., 1926, **9**, 861-879; Abst. Chem. Absts., **21**, 953-954.

Biometric, clinical and laboratory experiments prove that the adrenal cortex and not the medulla promotes body growth by a morphogenic hormone produced in its cells. Since the effect is less than that of the thyroid and of the hypophysis, possibly even less than that of the thymus, the admixture of large proportions of adrenal in pluriglandular preparations employed in growth deficiencies is not justified. Cortex alone should be used in view of the antagonistic and harmful effect of adrenaline in continued use.

Pharmacological effect of ephedrine. Kreitmair (H.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1927, **120**, 189-228; Abst. Chem. Absts., **21**, 1498.

The effects of ephedrine were analyzed through study of its action on blood pressure, heart action, on the vessels, on the respiratory center and on the bronchi, on the pupils, the intestine and the uterus, on the secretory activity of glands and on the blood sugar. Blood pressure is increased by small doses, lowered by large doses. Heart action is stimulated by small, inhibited by large doses. The blood vessels are constricted. Small doses stimulate the respiratory center and dilate the bronchi. Pupils are dilated. The action

of intestinal muscle is inhibited by small doses more than by larger ones. Any effect on glandular secretion is masked by the effect on the vessels. Ephedrine causes but little change in the blood sugar. The toxicity is not high. Ephedrine is destroyed in the body much more slowly than is adrenaline, and its effects persist for a correspondingly longer time. It is relatively insusceptible to the digestive fluids, does not deteriorate quickly and can be sterilized.

Spectrophotometric study of adrenaline. Lopez (J. M.), Anales soc. cient. Argentina, 1926, **101**, 133-154; Abst. Chem. Absts., **21**, 1129.

The ultra-violet spectra of natural and synthetic adrenaline-HCl are identical. The maximum absorption is 2780. The method is suitable for the determination of adrenaline.

Study of epinephrine. Maxenchs (A. T.), Ars Medica (Barcelona), 1927, **3**, 1; Abst. J. Am. M. Ass., **88**, 1609.

Maxench's experiments on dogs apparently show that epinephrine by mouth causes a transitory increase in blood sugar. This increase is proportional to the dose. The drug should preferably be given on an empty stomach. When given orally, five to ten times as much epinephrine is required as when it is injected. As toxicity is almost nil when it is given by mouth, the drug can be used concentrated in an isotonic solution, either Ringer's or a sodium chloride solution.

Does adrenaline exist in a totally free state in fresh suprarenal capsules? Mouriquand (G.) & Leulier (A.), Compt. rend. Soc. de biol. (Par.), 1926, **183**, 1353-1355; Abst. Chem. Absts., **21**, 954.

Guinea pigs in series of 6 each were killed and the suprarenals were removed as quickly as possible. These were divided into two lots, A and B, made up of equal numbers of right and left glands. Both lots were weighed immediately, and A was ground with anhydrous Na_2SO_4 to a powder, was allowed to macerate 30 minutes, when it was tested for adrenaline by the method of Bailly. B was placed in a vacuum desiccator with H_2SO_4 and after 24 hours was tested for adrenaline by the same method. A showed a faint trace of adrenaline; B gave from 0.15 to 0.26 gm. of adrenaline per kgm. of fresh material. Apparently adrenaline does not exist totally free in more than traces of the suprarenals.

Gases of the blood in suprarenal insufficiency. Pico (O. M.) & Deulofeu (V.), Compt. rend. Soc. de biol. (Par.), 1926, **95**, 1505; Abst. J. Am. M. Ass., **88**, 1118.

The authors made observations on suprarenalectomized dogs. The oxygen capacity of the blood increased, probably in connection with concentration of blood corpuscles. Saturation of the venous

blood with oxygen decreased, owing, presumably, to reduction in the volume of the blood and to slowing of the blood stream. The carbonic anhydride diminished, especially in the arterial blood, because of hyperpnea. The changes in the blood resemble those described by Henderson in shock, which result finally in acapnia.

Comparative variations in the content of the suprarenals in water, fatty acids and cholesterol in the normal guinea pig, and in the guinea pig under a diet deficient in the antiscorbutic vitamin. Randoin (L.) & Michaux (A.), Compt. rend. Soc. de biol. (Par.), 1926, **183**, 1055-1057; Abst. Chem. Absts., **21**, 1139.

In the adult normal guinea pig the suprarenals contain an average of 5.9 gm. of cholesterol per 100 gm. of fresh organ when on a natural diet and 5.07 gm. with a complete artificial diet; they contain 8.87-8.83 gm. of fatty acids and 68.9-68.4 gm. of H_2O per 100 gm. of fresh organ. On a diet deprived of the antiscorbutic vitamin the cholesterol content falls and toward the end reaches 2.63-2.78 gm. per 100 gm. The fatty acids diminish at the beginning, then become normal and even greater than under a complete diet. The water content remains about constant.

Diagnosis of primary suprarenal tumors. Schmieden (V.) & Peiper (H.), Arch. f. klin. Chir. (Berl.), 1926, **143**, 491; Abst. J. Am. M. Ass., **88**, 1610.

Five cases of primary tumor of the suprarenal body are described, one a blood cyst in a child 5½ months old. In the three cases in which it was employed, pneumo-peritoneum led to correct diagnosis, either with certainty or great probability. The authors consider it of the greatest value in the diagnosis of these tumors. By control of the vascular supply in situ the origin of the tumor in the suprarenal body may be determined during operation. Precocious puberty is seen in children, sex inversion in women with carcinoma of the cortex. Crises of pain are occasioned by pressure of suprarenal tumor on the thoracic or lumbar nerve roots. Bronzing of the skin is a not unusual symptom. Hematuria may be present.

The influence of the thyroid and of insulin on the oxydases in different organs. Mori (K.), Folia Endocrinologica Japonica (Kyoto), 1927, **2**, 40-41.

Studies were made on the influence of the thyroid and of insulin on the oxydases in the heart, the liver and the kidney, employing the histological method of Gierke and Gräff and the chemical method of Vernon. In the normal rabbit, the heart possesses a more marked oxydizing power than the kidney and liver. Insulin injected into the veins of the normal rabbit produces a slight augmentation of the oxydase reaction. This augmentation is greater

in the heart than in the kidney and is inconstant in the liver. The combined injection of glucose and insulin in the normal rabbit produces a marked augmentation of oxydase reaction. Consequently, although insulin alone can stimulate the intercellular oxidation, an increase of the amount of glucose in the tissues causes a greater effect. By histological examination the intravenous injection of thyroid extract causes a marked augmentation of the oxydases in all organs. But according to chemical examinations the results are positive only in the heart and kidney; they are indefinite in the liver. The simultaneous injection of insulin and of thyroid extract produces a striking augmentation of the oxydases by histological examination. In this case the augmentation is greater than the total of the two augmentations given by the separate injections. By chemical examination the augmentation in the heart and the kidney alone is a little greater than that in the case of the two separately made injections; in the liver it is indefinite. All the organs in the rabbit submitted to the thyroid treatment are richer in oxydase than those of the controls. The injection of insulin in the hyperthyroid rabbit produces a marked augmentation in all organs. The ablation of the thyroid provokes a diminution of the oxydases in all organs; the intravenous injection of insulin in the thyroidectomized rabbit produces a slightly smaller augmentation of the oxydases than in the normal rabbit. That is to say, the decrease of intercellular oxidation produced by thyroidectomy is compensated for by the injection of insulin at the normal level or a little above. The conclusion is made that there exists a synergism between the thyroid hormone and insulin as to the quantity of the oxydases of the tissues.—R. R. Durant.

Histological modifications in ovarian grafts (Le modifiche istologiche dei trapianti ovarici negli animali). Calvanico (R.), Internat. Rass. di Clin. e. Terap. (Napoli), 1926, **7**, 19.

The progressive histological changes in ovarian grafts were studied in an attempt to determine whether the interstitial gland or the germinative tissue is source of a hormone in ovarian transplantation. Forty female dogs and 10 female goats were used. The grafts were severally examined after 1 week, 10 days, 20 days and 40 days. The conclusion reached is that the ova and the germinative tissue are the first to disappear: that the interstitial gland, while lasting longer, undergoes some definite changes, which clearly show its relation to the reticulo-endothelial system.—G. V.

Castration in bats (Les effets de la castration chez les chéiroptères). Courrier (R.), Compt. rend. Soc. de biol. (Par.), 1926, **94**, 1368; Abst. Physiol. Absts., **12**, 117.

In bats, after castration in December, the accessory glands (prostate, etc.) remain unchanged if the animals are kept at a low

temperature hibernating, but undergo involution if the outside temperature is raised to 20° C.

Sex hormone from placenta ["feminin"] (Beitrag zur Kenntniss eines Sexaulhormons der menschlichen Placenta). Glimm (E.) & Wadehn (F.), Biochem. Ztschr. (Berl.), 1926, **179**, 3-18; Abst. Physiol. Absts., **12**, 116.

Preparation of a sex hormone from placenta by ether extraction is described. The increase in weight of the virgin rabbit uterus within a few days of the administration of the hormone is a useful qualitative test of the activity of preparations; 5 to 10 mouse units have a detectable effect, and 0.1 to 0.2 mgm. of the dry preparation corresponds to 1 mouse unit, 500 to 1,000 units being obtained from 1 kgm. of placenta. The presence of two hormones, one causing growth of the uterus and the other effecting the oestrus cycle, was not confirmed. Some activity was demonstrated in extracts of corpus luteum, but not in other tissues. The hormone may be administered orally or subcutaneously, the latter method being more effective. Large doses of the impure hormone damage the male generative organs.

The ovarian hormone (Zur Kenntnis des Ovarialhormons). Hartmann (M.), Klin Wchnschr. (Berl.), 1926, **5**, 2152-2154; Abst. Physiol. Absts., **12**, 116.

The author describes the method he has used in an attempt to isolate the ovarian hormone from the extract obtained by Frankel and Herrmann's method. After removal of several inactive fractions, the residual substances were distilled in a high vacuum (boiling point about 185° C.). The distillate was very active. On saponification it gave a number of unsaturated fatty acids of the C_n series. These were all inactive, but an unsaponifiable fraction still possessed considerable activity. In high vacuum it boiled at 145° C. and contained: C, 81.65 to 82.00%; H, 11.11 to 11.75%. It was unsaturated, but its structure has not yet been determined.

Histological changes in the testis of the guinea pig during scurvy and inanition. Lindsay (Blanche) & Medes (Grace), Am. J. Anat. (Balt.), 1926, **37**, 213-236; Abst. Chem. Absts., **21**, 945.

A diet deficient in vitamin C, or a diet containing sufficient A, B and C, but inadequate in total amount of food, both lead to degeneration of the seminal epithelium, unaccompanied by any marked change in the intertubular tissue. In young guinea pigs lack of C also retards development.

Emmenagogue action of the ovarian hormone. Loewe (S.), Klin. Wchnschr. (Berl.), 1927, **6**, 59; Abst. J. Am. M. Ass., **88**, 1362.

Loewe points out that the ovarian hormone promotes only the

building up of endometrium. Menstruation, which is the destructive phase, is due to cessation of this influence. Therefore the therapeutic administration of the hormone should be interrupted periodically to obtain an emmenagogue effect. Some cases of amenorrhea might be due perhaps to overproduction or overdosage of the hormone—rather than to its absence. The commercial preparations contain too little hormone to be active in castrated women. About 2,000 mouse units would have to be injected daily to obtain an effect. In mere hypofunction of the ovaries, smaller doses (perhaps 100 units) might help.

A lipo-gel reaction exerted by follicular fluid upon spermatozoa and its significance (Lillie's Reaction). Popa (G. T.), Biol. Bull. (Lancaster), 1927, **52**, 223-237.

When sperm suspensions are injected with follicular fluid taken from Graafian follicles, a coagulation is secured. The reaction is not produced by other liquids of the body, and is interspecific.

—M. O. Lee.

The corpus luteum in the hen and in mammals. Ramírez (E.), Revista Mexicana de Biología (Mexico City), 1926, **6**, 205; Abst. J. Am. M. Ass., **88**, 1120.

From an extensive study of the brooding hen, Ramírez concludes that the pregnant condition in mammals is already outlined in the hatching of birds. Brooding hens also possess a true homologous corpus luteum. Physiologic research of this type on birds would seem a promising field.

Ovarian hormone and the genitalia (Ovarialhormon, Wachstum der Genitalien, sexuelle Frühreife). Zondek (B.) & Aschheim (S.), Klin. Wchnschr. (Berl.), 1926, **5**, 2199-2202; Abst. Physiol. Absts., **12**, 118.

The water-soluble, dialysable hormone, prepared by the authors from ovary and placenta, and named "folliculin," has now been shown to produce growth of the uterus in immature mice. The average weight of the genitalia of mice treated for 14 days was 81 mgm., compared with 20 mgm. for control animals. The hormone also excites oestrus, and this condition is maintained so long as the hormone is administered. It does not produce maturity in the ovaries of immature mice, nor does it give rise to increased growth of the bones.

Action of pituitary extract on metabolism. Castex (M. R.) & Schteingart (M.), Compt. rend. Soc. de biol. (Par.), 1926, **95**, 1512; Abst. J. Am. M. Ass., **88**, 1118.

Castex and Schteingart administered extract of the posterior pituitary lobe to two healthy persons, to six patients with disease

of the thyroid, to two with disease of the pituitary, and to one diabetic patient. In ten, the basal metabolism increased; in one instance the increase was 27%. The metabolic changes were more pronounced in persons with a thyroid disturbance than in healthy persons. In patients with pituitary insufficiency the basal metabolism remained sometimes unaffected.

Hypophyseal colloid and cerebro-spinal fluid (Colloide hypophysaire et liquide cephalo-rachidien). Collin (R.), Compt. rend. Soc. de biol. (Par.), 1926, **95**, 107; Abst. Physiol. Absts., **12**, 115.

Histological evidence from the duck that colloid passes from the posterior lobe of the pituitary through the infundibulum and the ependyma into the cerebro-spinal fluid in the infundibular recess.

Diabetes insipidus. Depisch (F.) & Högler (F.), Wien. Archiv. f. innere Med. (Berl.), 1927, **13**, 509; Abst. J. Am. M. Ass., **88**, 1528.

Five cases of diabetes insipidus fit into neither the hyperchloremic nor the normochloremic type. Pituitary extracts proved beneficial in all cases.

Changes in the pituitary after section of the right vagus. Eaves (E. C.) & Clark (G. A.), J. Physiol. (Lond.), 1926, **62** (Proc.) i.

A preliminary communication based on the possibility that tonic inhibitory fibers to the islets of Langerhans exist in the right vagi of rabbits. After vagotomy, the pituitary was increased in size with histological changes similar to those occurring after insulin injection. It is suggested that these changes are due to increased insulin production occurring after removal of tonic inhibition.

—C. I. R.

Studies on the anterior lobe of the pituitary body. Johns (W. S.), O'Mulvenny (T. O.), Potts (E. B.) & Laughton (N. B.), Trans. Roy. Soc. Can., 1926, **20**, Sect. V, 243-245.

Protein-free aqueous extracts of ox anterior pituitary gland, from which the intermediate and posterior part had carefully been removed, when injected into healthy dogs produced hyperglucemia, glucosuria and polyuria. Intravenous injections into dogs and rabbits produced a slight rise in blood pressure. Successive injections always produced pressor effects. No effect was produced on rabbit- or guinea-pig-uterus strips, indicating that the active substance is different from those from the intermediate and posterior portions of the pituitary.—A. T. C.

Effect upon the intestine of extract of the posterior lobe of the hypophysis. Kaufmann (Margot), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1927, **120**, 324-329; Abst. Chem. Absts., **21**, 1498.

Extracts of the posterior lobe which are free of histamine have but a very slight stimulating effect on the small intestines of the rabbit or cat. The ileum reacts more strongly than the jejunum. On the large intestine an inhibitory effect is manifest, and the inhibiting substance is destroyed by alkali. This inhibition is but transitory wth low concentrations, and is followed by stimulating action. The active substance is present in the pars intermedia and in slight amounts in the pars neuralis. Apparently it is not identical with the substance which increases the blood pressure, stimulates the uterus or functions as an antidiuretic.

The pituitary gland and cholesterol metabolism. Moehlig (R. C.) & Ainslee (Harriet B.), Ann. Clin. Med. (Balt.), 1927, **5**, 772-779.

The authors believe that the pituitary gland regulates cholesterol metabolism and the tissues of mesenchymal origin. Arteriosclerosis, hypertension, certain types of nephritis, disturbances in blood volume, cholelithiasis, diabetes and uterine fibroids are found to have important relation to states of pituitary hyperfunction and hypofunction.—M. O. Lee.

Posterior pituitary extract and cholesterol metabolism. Moehlig (R. C.) & Ainslee (Harriet B.), Am. J. Physiol. (Balt.), 1927, **80**, 649-651.

Pituitary extract was injected in 1 cc. doses into 20 rabbits for a period of ten days. The blood cholesterol was increased in 17 of the 20 cases. The average for the whole series was about 31% higher after than before the injections.—R. G. H.

The effect of pituitrin on blood sugar. Tingle (C. D.) & Imrie (C. G.), J. Physiol. (Lond.), 1926, **62**, (Proc.) ii-iii. A preliminary report.

In a case of diabetes insipidus three subcutaneous injections of 0.5 cc. of pituitrin resulted in an increase in blood sugar, in each instance, of more than 100% in a half hour with return to normal in 2 to 3 hours. This effect is greater than that from 50 gm. of glucose. The fasting level of blood sugar in the patient was below the average. In normal subjects similar but less pronounced effects were obtained, except that after return to the initial level blood sugar continued to fall after one and one-half hours but rose again at the end of 3 hours. Pituitrin with glucose caused a rise of about 150% in an hour with return to the initial level in 2 hours, but a fall below normal thereafter. Pituitrin given an hour after glucose

produced approximately the same results. Pituitrin followed in a half hour by glucose gave results suggesting that the pituitrin effect occurred at once, the glucose effect somewhat later. The authors suggest that when blood sugar is raised, the pituitrin effect is delayed until it begins to fall again. In three cases of diabetes mellitus, pituitrin caused a fall in blood sugar in a half hour with return to the original level in 2 to 3 hours. No increase occurred in these cases.—C. I. R.

Changes in composition of blood in pernicious anemia. Murphey (W. P.), Monroe (R. T.) & Fitz (R.), J. Am. M. Ass. (Chicago), 1927, **88**, 1211-1214.

Changes were noted in the composition of the blood in ten patients with pernicious anemia, treated by a diet rich in liver. The results corroborate Minot and Murphy's observations that under proper dietetic care a prompt, rapid and distinct remission of the anemia is produced in each instance. The diet appeared to cause the delivery of new, young red blood cells from the bone marrow into the general circulation, as evidenced first by a prompt increase of the reticulocytes in the circulating blood. At about the time that there was evidence of a marked reaction in the bone marrow, there was a decrease of bile pigment concentration in the serum, as manifested by a fall in the icteric index. Coincidently there was an increasing red blood cell count and hemoglobin concentration, accompanied by a progressive growth in the blood tissue as a whole, as estimated by blood volume determinations. The morphologic appearance of the red corpuscles under treatment became normal, or essentially so; the color index finally became 1 or less than 1; the average cell volume diminished and approached normal; the volume index and the "stroma" index became normal. The diet did not produce changes in the nonprotein nitrogen of the plasma or in the plasma protein. The protein of the corpuscles, however, increased notably, and in almost direct proportion to the increasing hemoglobin concentration.—Author's Summary.

Diabetic acidosis with negative ferric-chloride reaction in urine. Appel (K. E.) & Cooper (D. A.), Am. J. M. Sc. (Phila.), 1927, **173**, 201; Abst. J. Am. M. Ass., **88**, 1597.

An analysis was made of the records of five patients with diabetes mellitus, who at some time in the course of this disease presented the unusual combination of a low carbon dioxide content of the plasma with a negative ferric chloride in the urine. As an explanation of an absent ferric chloride reaction in the urine in threatened diabetic coma, in advanced diabetic coma under treatment, in diabetic coma with considerably increased blood ketones, the authors suggest that it is probably due to temporary renal impairment usually on a basis of dehydration.

Surgery, diabetes and insulin. Chabanier (H.), Lebert, Lumiére & Lobo-Onell, Presse méd. (Par.), 1927, **35**, 210; Abst. J. Am. M. Ass., **88**, 1524.

The authors use insulin in prevention and treatment of acetonemia in surgical patients with diabetes. In external lesions with diabetes, it may be advantageously employed in general and in local treatment. It can be applied in the form of an ointment or a powder. The ointment is composed of 30 cc. of insulin, 1.5 gm. of zinc oxide, 45 gm. of wool fat and 90 gm. of petrolatum. Compresses with the ointment are renewed daily. If insulin powder is used, a compress with petrolatum is applied above the powdered area. Surprisingly good results were obtained in diabetic patients with operative wounds, trophic ulcerations of nervous origin, varicose ulcers, gangrenes, also with anthrax and furunculosis.

Influence of insulin on liver and muscle glycogen in the rat under varying nutritional conditions. Barbour (A. D.), Chaikoff (I. L.), Macleod (J. J. R.) & Orr (M. D.), Am. J. Physiol. (Balt.), 1927, **80**, 243-272.

White rats, weighing between 110 and 150 grams, were used in the experiment. It was found that after 24 hours' starvation the blood sugar averaged 0.106%, the liver glycogen 0.16%, and muscle glycogen 0.30.% After 48 hours' starvation the values were: blood sugar, 0.103%; liver glycogen, 0.32%, and muscle glycogen 0.25%. The results on individual rats in each group varied within a narrow range of the average (probable error not above 0.05), except in the case of the liver glycogen after 48 hours' starvation, in which case the probable error was 0.110. The increase in liver glycogen after 48 hours is considered to be due to the accentuation of a process of glyconeogenesis setting in after the original stores of glycogen in the liver have been exhausted. Injection of sub-convulsive doses of insulin in rats from whom food has been withheld for 48 hours, invariably caused a decrease in percentage of glycogen in the liver, in the first hour after injection. After the injection of 1 unit per kgm., this returned to the normal in about 1½ hours, and rose decidedly above it in 2 hours, the glycogen of the muscles at both of these periods being definitely decreased. After somewhat larger but still sub-convulsive doses of insulin (2 to 3 units per kgm.) the decrease in liver glycogen became more pronounced and the return to the normal level retarded, although recovery became quite evident before there was any demonstrable increase in blood sugar. There was a pronounced decrease in the muscle glycogen after these somewhat larger doses. No evidence of hypoglycemic symptoms appeared in any of these animals. After feeding previously fasted animals on a standard diet containing abundance of starches, the following changes were observed: the blood sugar curve rose steadily until it gained a level of between 0.15 and 0.16%, which was

reached in about an hour after feeding, and maintained for between 5 and 6 hours; the glycogen in the liver steadily rose from the starvation level until after 6 hours four per cent was present; the muscle glycogen during the same period rose to about 0.40%. When moderate amounts of insulin were injected one hour after feeding the deposition of glycogen in the liver was definitely retarded at all periods up to 3 hours after the injection of insulin. The glycogen of the muscles in these animals did not meanwhile deviate beyond the experimental error involved in the observation in the uninjected controls. In later periods, namely, 3 to 5 hours after injection, the muscle glycogen might or might not be somewhat higher. When very large doses of insulin were injected into fed rats the inhibitory effect on glycogen formation in the liver became more marked and the percentage in the muscles became definitely greater than in the controls, the total gained by the muscles being of about the same magnitude as the total deficit in the liver. It is concluded that after active absorption of carbohydrate has been proceeding for some time large doses of insulin cause more glycogen to be deposited in the muscles, this being accompanied by an approximately corresponding decrease in the amount deposited in the liver. Under the same conditions smaller doses of insulin, while having the same effect on the glycogen of the liver as larger ones, cause no demonstrable change in the glycogen of the muscles. In fasted animals insulin always causes a decrease in the glycogen content of both liver and muscles, but before there is any demonstrable recovery in blood sugar the glycogen of the liver returns to or about the initial level.—Authors' Summary.

Blood calcium as affected by insulin. Brougher (J. C.), Am. J. Physiol. (Balt.), 1927, **80**, 411-415.

In both normal and parathyroidectomized dogs the blood calcium is increased for a period of two and one-half hours following the administration of insulin.—Author's Summary.

On the metabolism of dihydroxyacetone in pancreatic diabetes. Campbell (W. C.) & Markowitz (J.), Am. J. Physiol. (Balt.), 1927, **80**, 561-575.

Experiments with the triose, dihydroxyacetone, on depancreatized animals have shown that it is not metabolized in the absence of insulin but forms glucose and is excreted quantitatively as such. It raises the blood sugar of these animals and its conversion to glucose requires no insulin. Though its respiratory quotient is unity it does not raise that of the depancreatized dog when administered in adequate amounts without insulin. It is not antiketogenic in these animals. There is no evidence that it is an intermediary compound in the catabolism of glucose.—Authors' Abstract.

"Synthalin." De Jong (D.), Nederl. Tijdschr. v. Geneesk. (Amst.), 1927, **71**, 541; Abst. J. Am. M. Ass., **88**, 1366.

Frank, Nothmann and Wagner have recently described a synthetic substitute for insulin. Studying the blood sugar effect of aminobuthylenguanidin, aminopenthylenguanidine and aminohexylenguanidine, they found that lengthening the methylene chain in the molecules of guanidine compounds increased the hypoglycemic effect of the substances and decreased the toxic effect. In this way they prepared a compound with somewhat slower but more lasting action than insulin, which they call "synthalin." De Jong studied the properties of the preparation on two diabetic patients, aged 70 and 61. Peroral administration of "synthalin" decreased the glycosuria, in proportion to the amount administered; the decrease was 0.40 and 0.55 gm. of dextrose, respectively, per mgm. of "synthalin." The blood sugar showed also a regular decrease. The preparation had a cumulative effect which lasted for 24 hours, and which was first noticeable in a few hours after the administration. It cannot, therefore, be used in diabetic coma, where a rapid decrease of the blood sugar is desired. It is especially useful in treatment of patients with a high insulin resistance. The great advantage of "synthalin" is that it can be administered perorally.

Tolerance to different foods in diabetes. Depisch (F.), Wien. Archiv. f. innere Med. (Berl.), 1927, **13**, 653; Abst. J. Am. M. Ass., **88**, 1528.

The author tested six diabetic patients for their tolerance to proteins, cereals and mixed diets. Cereals alone were tolerated better than a mixed diet. A little over one-half of the patients had a higher tolerance for a protein diet than for a mixed diet. The retention of food reserves is one of the sources of error. He believes that over longer periods the tolerance calculated according to the dextrose value of the food might be the same.

The effects of lowered body temperature and of insulin on the respiratory quotients of dogs. Finney (W. H.), Dworkin (S.) & Cassidy (G. J.), Am. J. Physiol. (Balt.), 1927, **80**, 301-310.

There is a fall in the respiratory quotient of a dog immediately after the administration of amytal. The respiratory quotient returns to its original value in from 30 to 60 minutes. The metabolic rate is greatly reduced by amytal anesthesia. Lowering the body temperature of a dog is in itself sufficient to cause the respiratory quotient to fall to a level as low as 0.032, provided that shivering has been suppressed. Even while the animal is shivering, the respiratory quotient may fall to a level far below 0.70. Therefore, lowering the body temperature of an animal causes a change in the character of its metabolism. The occurrence of shivering is asso-

ciated with a rise in the respiratory quotient indicating increased utilization of carbohydrate. The abolition of shivering, whether by means of insulin, curare, lowered body temperature, or anesthesia, causes the respiratory quotient of a dog to fall. The administration of insulin to a cooled dog that is not shivering causes the respiratory quotient to rise.—Authors' Summary.

Glycosuria after insulin (Glykosurie durch Insulin). Fricke (G.), Klin. Wchnschr. (Berl.), 1926, **5**, 1927-1928; Abst. Physiol. Absts. **12**, 43.

Dogs were given 60 to 100 gms. cane sugar, and at the same time 20 to 35 units of insulin. The hourly excretion of reducing substances in the urine was followed, and it was shown that, compared with control experiments in which no insulin was given, a definite glycosuria was caused by the insulin. The insulin caused the usual fall in blood sugar. In an experiment on himself, in which 350 gms. cane sugar and 140 units of insulin were taken, the author found only a small increase of reducing substances in the urine. The author suggests that the glycosuria of pregnancy and renal diabetes may be due to a hyperfunction of the pancreas.

Maximum hypoglucemia without the use of Insulin. II. Geiger (E.) & Szirtes (L.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1926, **119**, 1-23; Abst. Chem. Absts., **21**, 1494-1495.

Rabbits with the splanchnic sectioned may be sensitized by a diet of hay and beets so that the administration of atrophine or coli toxin causes a reduction in blood sugar. Apparently this diet causes a profound inhibition of the glyconeogenesis. The symptoms of the hypoglucemia can readily be abolished by injections of adrenaline or sugar. They occur only in animals with a sectioned splanchnic since in normal animals the adrenals exert a regulatory function. The effects of atropine on the concentration of blood sugar involves two factors; in normal animals it causes a hyperglucemia through a central stimulation; in the animal with the splanchnic sectioned it causes a hypoglucemia through inhibition of glyconeogenesis. The symptoms associated with the latter correspond almost exactly to those observed following the injection of insulin. The ensuing convulsions are not due to the hypoglucemia as such, but are referable to disturbances in carbohydrate metabolism. Hypothermia results from the carbohydrate impoverishment, and the latter, in turn, deranges the protein metabolism, this augmenting nitrogen excretion.

Xanthoma diabeticorum: Unusual process of involution. Goldstein (E.) & Harris (J.), Am. J. M. Sc. (Phila.), 1927, **173**, 195; Abst. J. Am. M. Ass., **88**, 1597.

A case of xanthoma diabeticorum is described, showing a pecu-

liar process of involution not previously mentioned in the literature. This occurred in a patient suffering from diabetes mellitus, to whom insulin was administered in the late stages of the disease. Three types of resolution went on simultaneously with little or no reference to the general condition: (a) The lesions on the palms disappeared completely; (b) those on the elbows coalesced and left large pigmented patches; (c) those on the legs and thigh underwent degenerative changes resulting in extensive scar formation—a process hitherto undescribed.

The effect of injected glucose on tolerance. Jordan (E. M.), Am. J. Phyiol. (Balt), 1927, **80**, 441-449.

Experimental evidence is given to support the hypothesis that incoming glucose acts as a stimulus to the islands of Langerhans, provoking a mobilization of insulin and thereby increasing the sugar-using power (tolerance) of the organism. As a corollary it has been demonstrated that when the tissues have obtained an optimal supply of insulin, additional insulin given by injection is inert. —Author's summary.

Endocrine pancreas function after ligature of ducts (Uber das Verhalten der endokrinen Pankreasfunktion nach Unterbindung des Ausführungsganges). Jorns, Klin. Wchnschr. (Berl.), 1926, 5, 2434-2437; Abst. Physiol. Absts. **12**, 108.

The observations of Mansfield on the increased sugar tolerance in dogs which results from ligature of the pancreatic ducts are confirmed. The author finds that the increased tolerance is first observed about two months after the operation, and lasts for about ten months. In rabbits the same phenomenon occurs, but only if the ligatured duct becomes patent again.

Insulin, arterial tension and glucemia. Jung (L.) & Auger (L.), Compt. rend. Soc. de biol. (Par.), 1927, **96**, 287-289; Abst. Chem. Absts., **21**, 1493.

Experiments with dogs showed that under ordinary conditions there is not necessarily any coincidence between the hypoglucemic and hypotensive actions of insulin; it has a hypotensive action independent of the diminution of the sugar in the blood.

Some influences of pancreatic hormone on the lymph. Katsura (S.) & Kozuka (K.), Tohoku J. Exp. Med., 1926, **8**, 91-106; Abst. Physiol. Absts., **12**, 108.

Insulin injected subcutaneously into rabbits in which the lymph is collected into cannulae from the thoracic duct and right lymphatic duct (thus not entering to the blood) causes a hypoglycaemia as low as 0.02% without any convulsions. If the lymph collected be

injected intravenously it does not cause convulsions, but a hyperglycaemia. Normal thoracic lymph injected intravenously causes hypoglycaemia. Insulin decreases the thoracic lymph sugar, while it increases the fat and lipoids. Adrenalin decreases the fat and lipoids of the thoracic lymph. In the normal starved animal the thoracic lymph fat and lipoids fluctuate somewhat, varying inversely as the variations in the blood and lymph sugar.

Action of Marienbad mineral water on the respiratory quotient and the metabolism of phosphorus in the diabetic. Kauffman-Cosla (O.) & Zorkendorfer (W.), Compt. rend. Soc. de biol. (Par.), 1927, **96**, 281-282; Abst. Chem. Absts., **21**, 1493.

By the administration of mineral water to the diabetic the respiratory quotient is raised by an increase in the elimination of carbon dioxide. This is paralleled by a diminution in the abnormal carbon constituents in the urine. At the same time there is a pronounced diminution of the elimination of urinary phosphorus.

Rapid disappearance from the blood of insulin injected intravenously. Kepinow (L.) & Lebert (S.), Compt. rend. Soc. de biol. (Par.), 1927, **96**, 371-374; Abst. Chem. Absts., **21**, 1493.

Dog A received an injection of insulin and in 3 minutes its blood was transfused to Dog B, previously bled. The sugar in the blood of A 1 to 3 hours after the transfusion was about one-half that in B. In a second experiment in which the transfusion was made in 30 seconds after the injection of insulin, the sugar in the blood of A for the 3 hours after the injection was markedly lower than in the blood of B. It is suggested that the insulin is fixed in tissues rich in glycogen.

The antiketogenic influence of insulin in diabetes mellitus. Killian (J. A.), J. Lab. & Clin. M. (St. Louis), 1926, **11**, 1132-1139; Abst. physiol. Absts., **12**, 43.

Observations on 7 cases of diabetes show that the administration of insulin causes an immediate decrease of the ketone bodies of blood and of urine, reaching a maximum in 4 to 6 hours. This decrease in ketosis is accompanied by a rise in the alkali reserve of the blood and a proportional increase in the blood pH. This influence of insulin is regarded as due to the more complete oxidation of the carbohydrates.

Insulin and diuresis. Klein (I.) & Rischawy (E.), Ztschr. f. d. ges. exper. Med. (Berl.), 1926, **51**, 652-672; Abst. Chem Absts., **21**, 963.

There is a close relationship between the changes brought about by insulin in the H_2O metabolism of a diabetic and the action of this hormone on carbohydrate metabolism.The reduction in the amount

of urine, decrease in NaCl concentration in the urine, fall in NaCl content in the blood and concentration of the blood are indications of the extrarenal H_2O and NaCl retention brought about in the diabetic by insulin. The salt retention is connected with the increased binding of H_2O in the tissues caused perhaps by increased combustion of carbohydrates or increased deposition of glycogen or decreased breaking up of glycogen under the influence of insulin. The H_2O and NaCl retention are more marked when insulin is given without carhohydrates. Several hours after giving insulin there is a marked increase in H_2O and NaCl diuresis which is as yet unaccounted for, but may be due to stimulation of the vegetative nervous system. In a normal individual insulin causes only a transitory inhibition of diuresis, but there is no abrupt rise in diuresis after some hours as in a diabetic and there is no marked diuretic effect after both insulin and carbohydrates are given as in the diabetic.

Insulin in hepatic diseases. Klein (O.) & Holzer (H.), Klin. Wchnschr. (Berl.), 1927, **6**, 157; Abst. J. Am. M. Ass., **88**, 1611.

Large doses of insulin (from 60 to 100 units daily) were administered to patients with diseases of the liver. The jaundice was influenced beneficially in almost all of them, including some with cirrhosis and cancer. The patients easily become hypoglycemic, even with a large carbohydrate intake.

Ability of the tissue cells to take up and fix sugar. Relation of tissue cells to the action of insulin and to diabetes. Kurokawa (T.), Tohoku J. Exptl. Med., 1926, **8**, 54-74; Abst. Chem. Absts., **21**, 954-955.

Absorption of sugar by body cells in the sense mentioned by Mendel, Engel and Goldscheider occurs in diabetic as in normal subjects. Such absorbed sugar is fixed only through healthy metabolism, and this fixation ability fails in the diabetic, in which the absorbed sugar again enters the circulation and finally appears in the urine. Insulin exercises no perceptible influence on the sugar-absorbing ability. On the other hand insulin promotes the sugar-fixation power whereby the organism is protected from an overflow of the blood sugar.

Increase in the insulin content of pancreatic venous blood after excitation of the vagus nerve. LaBarre (Jean), Compt. rend. Soc. de biol. (Par.), 1927, **96**, 193-196; Abst. Chem. Absts., **21**, 1484.

When the modified technic of Hedon was used, it was concluded that with 2 dogs in pancreatico-jugular anastomosis, if the peripheric end of the right vagus of the donor be electrically stimulated, the transfusion of pancreatic venous blood of this animal leads, in its congener, to a state of marked hypoglucemia.

It appears that the secretion of insulin in the venous blood of the pancreas increases under the influence of nerve modifications of vagal origin.

Existence of a physiologic insulinemia. LaBarre (Jean), Compt. rend. Soc. de biol. (Par.), 1927, **96**, 196-198; Abst. Chem. Absts., **21**, 1484.

By the transfusion of a relatively small quantity of pancreatic venous blood, the hyperglucemia in a dog previously depancreatized is reduced. The experiments also show that the blood issuing from the gland with its higher content of insulin has an antidiabetic action much more marked than blood from the normal carotid. The existence of a physiologic insulinemia is accordingly considered as proved.

The action of insulin in glycogen formation and its therapeutic application. Lawrence (R. D.), Quart. J. Med. (Oxford), 1926, **20**, 69-86; Abst. Physiol. Absts. **12**, 43.

Exercise lowers normal blood sugar slightly, but a diabetic blood sugar more markedly, and increases the action of insulin; but if a patient is accustomed to insulin, exercise without it increases the blood sugar, owing to glycogenolysis of the store formed under the action of insulin; but at the same time the arteriovenous difference is increased, showing that the muscles are utilizing glucose. In exercise with insulin much more of the glycogen store is utilized, resulting in late hypoglycemic symptoms. The insulin effect is more marked when the glycogen store is depleted, as in emaciated diabetic first coming under treatment; as the condition improves, more insulin will be required, but this does not imply a depreciation of the patient's condition. In a theoretical consideration of the action of insulin, the author concludes that its effect is anabolic, i.e., it acts by forming glycogen from glucose; its effect by increasing the carbohydrate metabolism in a diabetic is indirect, the increased metabolism following the increased amount of glycogen in the stores. The author considers that sugar can be formed from fat as well as protein; the former conversion is especially active when the glycogen stores are low, and ketosis then occurs, the ketone bodies being stages in the normal conversion of fat to carbohydrate. Insulin by supplying glycogen, the combustible carbohydrate, reduces the excessive conversion of fat (and protein) to carbohydrate and thus abolishes the ketosis. In treating a diabetic it is better for his comfort to have a carbohydrate store, even though this means a fluctuating blood sugar level and less chance of recovery of function by the islets of Langerhans.

Action of insulin on naphthalinic cataract. Michaïl (D.) & Vancea (P.), Compt. rend. Soc. de biol. (Par.), 1927, **96**, 65; Abst. J. Am. M. Ass. **88**, 1524.

Rabbits were given naphthalene by mouth daily. As soon as lesions appeared in the lens, insulin was administered. Naphthalene was continued. Insulin appeared to retard markedly the occurrence of cataract. In another series of animals, insulin treatment preceded and accompanied the administration of naphthalene. Insulin was found to increase the resistance of the animal's organism to acute naphthalene poisoning. In a third series of experiments, naphthalene was given until lesions started in the lens, whereupon it was replaced by insulin. This resulted in disappearance of the lesion in the lens. The cure was transient in some animals, durable in others. The clinical course of some senile cataracts and the course of cholesterolemia in these cases suggest an analogy with naphthalinic cataract. The authors believe that at least some senile cataracts may be of pancreatic origin.

Effect of insulin upon the carbon dioxide content in the arterial blood sugar level in rabbits poisoned by carbon monoxide. Mikami (S.), Tohoku, J. Exptl. Med., 1927, **8**, 378-383; Abst. Chem. Absts. **21**, 1494.

Insulin is capable of inhibiting the reduction of carbon dioxide content as well as hyperglucemia due to carbon monoxide poisoning. When it is applied to normal, non-poisoned rabbits, the carbon dioxide content in the arterial blood shows an inclination to reduce slightly.

The glycogen content of frog's muscle after injection of insulin and its relation to contraction. Olmstead (J. M. D.) & Harvey (J. M.), Am. J. Physiol. (Balt.), 1927, **80**, 643-648.

The muscles of frogs can be rendered practically free from glycogen by causing them to have prolonged and violent insulin convulsions, i.e., the glycogen content is less than 0.2 mgm. per gram of muscle, the limit of detectability by the method of analysis used (Plüger's). Yet under these conditions the muscle is able to contract for hours upon being stimulated in the intact animal with maximal shocks from an inductorium, the height of contractions being virtually the same as in the normal frog's muscle stimulated for the same length of time.—Authors' Abstract.

Danger of insulin hypoglycemia in children. Priesel (R.) & Wagner (R.), Klin. Wchnschr. (Berl.), 1927, **6**, 65; Abst. J. Am. M. Ass. **88**, 1362.

The authors believe that death from hypoglycemia in a diabetic child might be prevented if a large dose of dextrose were

injected immediately on the appearance of threatening symptoms; for instance, at least a 20 cc. of a 33% solution, intravenously. If considerable improvement does not take place instantaneously, they inject from 100 to 200 cc. of a 10% solution beneath the skin. When the patient regains consciousness, he should be given fruit or bread.

The presence of insulin-like substances in malignant tumors (La existencia de insulinoides en los tumores malignos). Roffo (A. H.) & Correa (L. M.), Bol. inst. de med. exp. de Buenos Aires, 1926, **2**, 969-972; Abst. Physiol. Absts. **12**, 108.

A sarcoma of the rat has yielded from 500 grams of material 8 to 12 units of a substance with similar properties to those of insulin.

Glycemia and diseases of the stomach. Rosenberg (M.) & Kallner (A.), Deutsche med. Wchnschr. (Berl. & Leipz.), 1927, **53**, 183; Abst. J. Am. M. Ass. **88**, 1611.

Gastric ulcer or nervous irritability of the stomach was found only rarely in diabetes (in about 1% of the patients). About one-quarter of the patients with innocuous glycosuria had these disturbances. Lability of the vegetative nervous system might be the cause of both phenomena in the latter group.

Diabetes mellitus and hypoglycaemia. Rosendahl (G.), Acta Medica Scandinavica (Stockholm), 1927, **66**, 100-108.

A case of diabetes mellitus is reported in which repeated attacks of hypoglycemia were observed. The first attack occurred suddenly after treatment with insulin, but the last attacks occurred in spite of rather high carbohydrate diets and no insulin. Only glucose injections alleviated the symptoms. Although slight alkalosis was observed, an acetonuria, high NH_3, and excess of chloride and nitrogen were present in the urine. The patient died in hypoglycemia. At autopsy a completely sclerotic pancreas and a slight liver cirrhosis were found. Rosendahl suggests a liver insufficiency as the cause of hypoglycemia in such cases.

—M. O. Lee.

The influence of insulin on the acetaldehyde formation in the body of animals. Supniewski (J. V.), J. Biol. Chem. (N. Y.), 1926, **70**, 13; Abst. Physiol. Absts. **12**, 46.

Acetaldehyde was determined in the blood and organs of several animals, including the rabbit, cat, and dog, by the method of Bougault and Gros. Insulin was found to increase the aldehyde content of the organs both in vivo and in vitro. The blood of depancreatised dogs contained 0.2 to 0.4 mgm. of total aldehyde

per 100 gm. of blood, the normal figure being less than 0.1. Insulin administration was found to abolish this excess. Administration of alcohol or aldehyde increased the amount of aldehyde in the blood. Insulin accelerated the subsequent return to normal.

Endocrine factors in oxalic acid metabolism. Viale (G.), Rev. sudamericana endocrinol. immunol. quimioterap., 1926, **9**, 967-977; Abst. Chem. Absts. **21**, 954.

Insulin injections do not alter the $C_2H_2O_4$ content of the blood of rabbits and dogs, but cause a marked decrease of its excretion in urine. The latter is also observed in diabetes. A considerable increase of oxalaturia appears as a result of adrenaline injections and of pancreatectomy. Daily adrenaline injections have an increasing influence on glucosuria. Phlorhizin diabetes has no noteworthy effect on $C_2H_2O_4$ excretion. Oxalic acid is an intermediate of sugar metabolism. Its production is controlled by the internal secretion of the pancreas. Insulin is indicated in oxalatemia.

Rôle of carbohydrate retention in hypertension. Weiler (E. S.), Semana méd. (Bs. Aires), 1927, **34**, 155; Abst. J. Am. M. Ass. **88**, 1525.

The author reviews his work on the rôle of carbohydrate retention in the etiology of arterial hypertension. According to his theory, hypertension, as well as obesity and diabetes, is a manifestation of insulin deficiency. Long before Wohl, Weiler had referred to the need of vitamins in diets prescribed for diabetic patients.

Increase in the insulin content of the pancreatic venous blood after hyperglucemia caused by the injection of glucose. Zunz (E.) & LaBarre (Jean), Compt. rend. Soc. de biol. (Par.), 1927, **96**, 421-423; Abst. Chem. Absts. **21**, 1489.

By the pancreatic-jugular anastomosis a transfusion experiment was made with dogs, which proved that the insulin content of the pancreatic vein is increased after an intravenous injection of a large dose of glucose.

Osteitis fibrosa. Mandl (F.), Arch. f. klin. Chir. (Berl.), 1926, **143**, 245; Abst. J. Am. M. Ass. **88**, 1610.

The relations between the parathyroids and diseases of the bone are discussed. Forty-four cases were collected from the literature in which enlargement of the parathyroids was associated with rickets, osteitis deformans, osteomalacia, senile osteoporosis or generalized osteitis fibrosa. The author describes a case in which he removed a parathyroid tumor on therapeutic grounds in a severe case of generalized osteitis fibrosa. The excretion of cal-

cium in the urine had decreased five-sixths a few days after the operation. The general condition underwent remarkable improvement, the pains became slight and came on only at times of changes in the weather. Motion has entirely returned in the joints of the extremities and the patient, who before the operation could neither stand nor walk, can now stand without difficulty and walks with a cane and a crutch. This case seems to destroy the validity of Erdheim's theory of compensatory hypertrophy on the part of the parathyroids. Animal experimentation aiming to produce pictures similar to osteitis fibrosa by trauma and washing out the marrow were negative. The pictures were obtained when coagulation of the blood was retarded by injections of citrate.

Hydrogen ion concentration and carbon dioxide content of blood of parathyroidectomized dogs. Wenner (W. F.) & Muntwyler (E.). Proc. Soc. Exper. Biol. & Med. (N. Y.), 1927, **24**, 480-482.

A condition of alkalosis does not exist either before or during tetany following parathyroidectomy. The conclusions are based on measurements of pH and carbon dioxide content of plasma and calcium content of serum in three dogs.—J. C. D.

Influence of experimental hypothyroidism upon gastric secretion. Chang (H. C.) & Sloan (J. H.), Am. J. Physiol. (Balt.), 1927, **80**, 732-734.

Thyroidectomy in two dogs caused an increase in the volume and acidity of gastric juice. Thyroid feeding before thyroidectomy caused a decrease of gastric secretion, both in amount and acidity. Thyroid feeding after thyroidectomy also depressed gastric secretion. The depression disappeared when thyroid feeding was stopped.—M. O. Lee.

Water metabolism in myxedema and exophthalmic goiter. Falta (W.) & Högler (F.), Wien. Archiv. f. innere Med. (Berl.), 1927, **13**, 547; Abst. J. Am. M. Ass. **88**, 1528.

The authors found sodium strongly hydropigenic and potassium and calcium antihydropigenic in myxedema. The water test diuresis was above normal. Preliminary administration of salty food increased the water and salt-water diuresis, while it inhibited it in normal individuals. In exophthalmic goiter patients, the opposite results were seen. They conclude that in these conditions the change is less one of the speed of salt transportation than one of the hydration condition of the colloids of the tissues.

Effect of potassium iodide and thyroid extract on thyroid gland of guinea-pig. Gray (S. H.), Haven (F. L.) & Loeb (Leo). Proc. Soc. Exper. Biol. & Med. (N. Y.), 1927, **24**, 503-505.

If guinea pigs are fed potassium iodide, their thyroid glands

show an increased number of mytoses with no change in the size of the acini. After the treatment has been continued for more than six weeks the mitotic figures decreases in number, the epithelium becomes lower, and the acini enlarge and are filled with solid hard colloid. In thyroid-fed guinea pigs, the epithelium is low, mitotic figures few, and the colloid hard. The author suggests that potassium idodide stimulates the gland to produce an excess of colloid. There being no call for this excess, it is eventually stored up in the gland in amounts sufficient to produce regressive changes. Thyroid feeding by supplying the body directly results in very rapid storage of colloid in the gland with similar regressive changes.—J. C. D.

On the innervation and secretory path of the thyroid gland. Hicks (C. S.), J. Physiol. (Lond.), 1926, **62**, 198-202; Abst. Physiol. Absts. **12**, 49.

In normal dogs thyroglobulin passes out of the thyroid by veins and lymphatics. The rate of secretion is uninfluenced by stimulation of the sympathetic, but appears to be increased on administration of iodine.

The effect of the administration of cod liver oil upon thyroparathyroidectomized dogs. Jones (J. H.), J. Biol. Chem. (N. Y.), **70**, 647 (1927).

Daily ingestion by mouth of 20 cc. of cod liver oil for two weeks before thyroparathyroidectomy prevented tetany and greatly increased the length of life in dogs. If the oil is given only after operation there is no effect. The ingestion of the oil had little effect on the change in blood calcium. Similar results were obtained by irradiation of the animals.—J. B. Brown.

Thyroid disease: Diagnostic value of the Kottman reaction in thyroid dysfunctions. Katayama (I.), Am. J. M. Sc. (Phila.), 1926, **172**, 84; Abst. J. Lab. & Clin. M. **12**, 713.

The basal metabolic rate is to be the most dependable laboratory index of thyroid activity. Increased thyroid secretion produces a lowering of the tolerance for carbohydrate, but there are numerous other conditions in which the tolerance for carbohydrate may be diminished. Hence the occurrence of high blood and urine sugar curve after the ingestion of glucose is not in itself indicative of hyperthyroidism. In hyperthyroidism, however, the blood and urine sugar curves after glucose furnish information concerning a phase of carbohydrate metabolism which is not gauged by the basal metabolic rate. The basis of the Kottman reaction is obscure, and hence it is difficult to say in what manner thyroid activity influences it. Such a reaction can only be accepted with skepticism. From the data reported in this paper it is evident that the results of the Kottmann reaction are not in accord with the

basal metabolism or the glucose tolerance. The retardation of the reduction of the silver iodode to silver occurs in many and various conditions patently not due to hyperthyroidism. Its diagnostic value in detecting hyperfunction or hypofunction of the thyroid is very dubious. It cannot be accepted as a substitute for the determination of the basal metabolic rate of glucose tolerance.

Synthetic thyroxin—clinical tests. Lyon (D. M.) & Redbead (F. A.), Edinb., M. J., 1927, **34**, 194-199.

Report of two cases treated with thyroxin produced according to the method of Harington and Barger. These cases showed an increase in basal metabolism of 1.85% to 3.43% per mgm. of drug and the physiological improvements to be expected from the administration of thyroxin.—J. C. D.

Ante-mortem protein decomposition after thyroidectomy (Beiträge zur Physiologie der Schilddrüse. X. Prämortaler Eiweisszerfall bei Schilddrüsenlosen Hunden). Mansfeld (G.) & Lanczos (A.), Biochem. Ztschr. (Berl.), 1926, **179**, 186-193; Abst. Physiol. Absts. **12**, 114.

In thyroidectomized dogs dying from starvation within a month of the extirpation, increased protein decomposition could not be detected in 3 out of 4 cases.

The effect of large doses of iodine on heat production in rabbits. Marine (D.), Deutch (M.) & Cipra (Anna). Proc. Soc. Exper. Biol. & Med. (N. Y.), 1927, **24**, 657-662.

Eighteen rabbits were treated with Lugol's solution or with potassium iodide and tested to see if they showed a change in heat production. Eleven showed no change, two a rise, and five a decrease. No relation between the response to treatment and the histological condition of the thyroid gland could be observed.

—J. C. D.

Effect of ergotamine tartrate on the heat production of normal and thyroidectomized rabbits. Marine (D.), Deutch (M.) & Cipra (Anna). Proc. Soc. Exper. Biol. & Med. (N. Y.), 1927, **24**, 662-664.

Ergotamine tartrate, a drug whose action neutralizes the action of adrenin, reduces the heat production of normal rabbits markedly and of thyroidectomized rabbits slightly.—J. C. D.

Relation of hypothyroidism to obstetrics and gynecology. O'Keefe (C. D.), South. M. J. (Birmingham), 1927, **20**, 375-379.

Hypothyroidism, in and around St. Louis, is a common disease among women. The patients present characteristic histories, physi-

cal findings, and metabolic changes, which make the diagnosis comparatively easy. Infection, normal pregnancy, abortions, miscarriages, and operations play an important role in the etiology of thyroid deficiency, the hypothyroidism in turn having a marked influence on pregnancy and sexual life in general. Severe menopause changes are due to glandular deficiency in general, and to thyroid in particular, and are not due to ovarian death alone. Relief from these disturbing symptoms through thyroid medication, providing the offending cause has been removed, is obtained in a very large percentage of cases. The cure depends almost entirely upon the duration of the disease.—Author's Abstract.

Is thyroidectomy the primary cause of the arrested development of skeletal muscle in cretin sheep? Simpson (Ethel D.), Am. J. Physiol. (Balt.), 1927, **80**, 735-738.

The non-development of muscle fibers in young sheep after thyroidectomy is considered as being due to the reduced bodily activity, rather than to the athyroid conditions. Control sheep, lethargic after being stunted by parasitic worms, showed the same non-development of striated muscle.—M. O. Lee.